Biophysical Chemistry and Theoretical Biophysics

Principles, Theory and Experimental Applications

Biophysics and Related Fields

Biophysics

Biophysics (also **biological physics**) is an interdisciplinary science that employs and develops theories and methods of the physical sciences for the investigation of biological systems. Studies included under the umbrella of biophysics span all levels of biological organization, from the molecular scale to whole organisms and ecosystems. Biophysical research shares significant overlap with biochemistry, nanotechnology, bioengineering, agrophysics and systems biology.

Molecular biophysics typically addresses biological questions that are similar to those in biochemistry and molecular biology, but the questions are approached quantitatively. Scientists in this field conduct research concerned with understanding the interactions between the various systems of a cell, including the interactions between DNA, RNA and protein biosynthesis, as well as how these interactions are regulated. A great variety of techniques are used to answer these questions.

Fluorescent imaging techniques, as well as electron microscopy, x-ray crystallography, NMR spectroscopy and atomic force microscopy (AFM) are often used to visualize structures of biological significance. Conformational changes in structure can be measured using techniques such as dual polarisation interferometry and circular dichroism. Direct manipulation of molecules using optical tweezers or AFM can also be used to monitor biological events where forces and distances are at the nanoscale. Molecular biophysicists often consider complex biological events as systems of interacting units which can be understood through statistical mechanics, thermodynamics and chemical kinetics. By drawing knowledge and experimental techniques from a wide variety of disciplines, biophysicists are often able to directly observe, model or even manipulate the structures and interactions of individual molecules or complexes of molecules.

In addition to traditional (i.e. molecular and cellular) biophysical topics like structural biology or enzyme kinetics, modern biophysics encompasses an extraordinarily broad range of research. It is becoming increasingly common for biophysicists to apply the models and experimental techniques derived from physics, as well as mathematics and statistics, to larger systems such as tissues, organs, populations and ecosystems.

Focus as a subfield

Biophysics often does not have university-level departments of its own, but has presence as groups across departments within the fields of molecular biology, biochemistry, chemistry, computer science, mathematics, medicine, pharmacology, physiology, physics, and neuroscience. What follows is a list of examples of how each department applies its efforts toward the study of biophysics. This list is hardly all inclusive. Nor does each subject of study belong exclusively to any particular department. Each academic institution makes its own rules and there is much overlap between departments.

- Biology and molecular biology - Almost all forms of biophysics efforts are included in some biology department somewhere. To include some: gene regulation, single protein

dynamics, bioenergetics, patch clamping, biomechanics.
- Structural biology - Ångstrom-resolution structures of proteins, nucleic acids, lipids, carbohydrates, and complexes thereof.
- Biochemistry and chemistry - biomolecular structure, siRNA, nucleic acid structure, structure-activity relationships.
- Computer science - Neural networks, biomolecular and drug databases.
- Computational chemistry - molecular dynamics simulation, molecular docking, quantum chemistry
- Bioinformatics - sequence alignment, structural alignment, protein structure prediction
- Mathematics - graph/network theory, population modeling, dynamical systems, phylogenetics.
- Medicine and neuroscience - tackling neural networks experimentally (brain slicing) as well as theoretically (computer models), membrane permitivity, gene therapy, understanding tumors.
- Pharmacology and physiology - channel biology, biomolecular interactions, cellular membranes, polyketides.
- Physics - biomolecular free energy, stochastic processes, covering dynamics.
- Agronomy Agriculture

Many biophysical techniques are unique to this field. Research efforts in biophysics are often initiated by scientists who were traditional physicists, chemists, and biologists by training.

Topics in biophysics and related fields

- Theoretical biophysics
- Mathematical biophysics
- Systems biology
- Medical biophysics
- Agrophysics
- Origin of Life

Molecular biophysics

- Biological membranes
- Cell membranes
- Bioenergetics
- Channels, receptors and transporters
- Enzyme kinetics
- Molecular motors
- Phospholipids
- Proteins
- Biofilms
- Supramolecular assemblies
- Nucleic acids

Cellular biophysics

- Cell division
- Cell migration
- Cell signalling
- Dynamical systems

- Electrophysiology
- Signaling
- Biochemical systems theory
- Metabolic control analysis

Techniques used in biophysics

- Atomic force microscopy
- Biophotonics
- Biosensor and Bioelectronics
- Calcium imaging
- Calorimetry
- Circular Dichroism
- Cryobiology
- Dual polarisation interferometry
- Electrophysiology
- Fluorescence
- Microscopy
- Neuroimaging
- Neutron spin echo spectroscopy
- Patch clamping
- Nuclear Magnetic Resonance Spectroscopy
- Spectroscopy, imaging, etc.
- x-ray crystallography

Other

- Animal locomotion
- Bioacoustics
- Biomechanics
- Biomineralisation
- Bionics
- Evolution
- Evolutionary algorithms
- Evolutionary computing
- Evolutionary theory
- Gravitational biology
- Mathematical biology
- Morphogenesis
- Muscle and contractility
- Negentropy
- Neural encoding
- Radiobiology
- Sensory systems
- Systems neuroscience
- Tensegrity
- Theoretical biology

Famous biophysicists

- Luigi Galvani, discoverer of bioelectricity
- Hermann von Helmholtz, first to measure the velocity of nerve impulses; studied hearing and vision
- Alan Hodgkin & Andrew Huxley, mathematical theory of how ion fluxes produce nerve impulses
- Georg von Békésy, research on the human ear
- Bernard Katz, discovered how synapses work
- Hermann J. Muller, discovered that X-rays cause mutations
- George Palade Nobel Laureate in physiology or medicine for protein secretion and cell ultra-structure from electron microscopy studies
- Linus Pauling & Robert Corey, co-discoverers of the alpha helix and beta sheet structures in proteins
- J. D. Bernal, X-ray crystallography of plant viruses and proteins
- Rosalind Franklin, Maurice Wilkins, James D. Watson and Francis Crick, pioneers of DNA crystallography and co-discoverers of the structure of DNA. Francis Crick later participated in the Crick, Brenner et al. experiment which established the basis for understanding the genetic code
- Max Perutz & John Kendrew, pioneers of protein crystallography
- Sir John Randall, X-ray and neutron diffraction of proteins and DNA
- Ronald Burge, X-ray diffraction of nerve myelin, bacterial cell walls and membranes
- Allan Cormack & Godfrey Hounsfield, development of computer assisted tomography
- Kurt Wüthrich Nobel Laureate in physiology or medicine for 2D-FT NMR of protein structure in solution[1]
- Paul Lauterbur & Peter Mansfield, development of magnetic resonance imaging
- Stephen D. Levene, DNA-protein Interactions, DNA looping, and DNA topology.
- Seiji Ogawa, development of functional magnetic resonance imaging

Other notable biophysicists

- Adolf Eugen Fick, responsible for Fick's law of diffusion and a method to determine cardiac output.
- Howard Berg, characterized properties of bacterial chemotaxis
- Steven Block, observed the motions of enzymes such as kinesin and RNA polymerase with optical tweezers
- Carlos Bustamante, known for single-molecule biophysics of molecular motors and biological polymer physics
- Steven Chu, Nobel laureate who helped develop optical trapping techniques used by many biophysicists
- Christoph Cremer, overcoming the conventional limit of resolution that applies to light based investigations (the Abbe limit) by a range of different methods
- Friedrich Dessauer, research on radiation, especially X-rays
- Julio Fernandez
- Govindjee, professor emeritus at the University of Illinois, research in photosynthesis and photosynthetic mechanisms by fluorescence and NMR methods
- Enrico Gratton research on frequency domain spectroscopy and correlation spectroscopy on biological and biomedical systems

- Stefan Hell, developed the principle of STED microscopy
- Richard Henderson, scientist at the MRC Laboratory of Molecular Biology, developed the use of cryo-EM to study membrane protein structures.
- John J. Hopfield, worked on error correction in transcription and translation (kinetic proof-reading), and associative memory models (Hopfield net)
- Martin Karplus, research on molecular dynamical simulations of biological macromolecules.
- Franklin Offner, professor emeritus at Northwestern University of professor of biophysics, biomedical engineering and electronics who developed a modern prototype of the electroencephalograph and electrocardiograph called the dynograph.
- Nicolas Rashevsky,[2] , former Editor of the first journal of mathematical and theoretical biophysics entitled " *The Bulletin of Mathematical Biophysics* " (1940--1973) and author of the two-factor model of neuronal excitation, biotopology and organismic set theory.
- Robert Rosen, theoretical biophysicist and mathematical biologist, author of: metabolic-replication systems, categories of metabolic and genetic networks, quantum genetics in terms of von Neumann's approach, non-reductionist complexity theories, dynamical and anticipatory systems in biology.[3]
- Benoit Roux
- Mikhail Volkenshtein, Revaz Dogonadze & Zurab Urushadze, authors of the first quantum-mechanical model of enzyme catalysis, supported a theory that enzyme catalysis use quantum-mechanical effects such as tunneling.
- John P. Wikswo, research on biomagnetism
- Douglas Warrick, specializing in bird flight (hummingbirds and pigeons)
- Ernest C. Pollard — founder of the Biophysical Society
- Marvin Makinen, pioneer of the structural basis of enzyme action
- Gopalasamudram Narayana Iyer Ramachandran, developer of the Ramachandran plot and pioneer of the collagen triple-helix structure prediction
- Doug Barrick, repeat protein folding
- Naomi Courtemanche, kinetics of leucine rich repeat protein folding
- Ellen Kloss, salt-dependence of leucine rich repeat protein folding
- Bertrand Garcia Moreno E., Dielectric Constant of Globular Protein 'hydrophobic' core
- Ludwig Brand, Time resolved fluorescence anisotropy decay in Biological systems

See also
- Important publications in **bio**physics
- Important publications in bio**physics**

Notes
[1] http://nobelprize.org/nobel_prizes/chemistry/laureates/2002/wuthrich-autobio.html
[2] http://planetmath.org/encyclopedia/NicolasRashevsky.html
[3] Robert Rosen's Research and Biography http://planetmath.org/encyclopedia/RobertRosen.html

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- Hobbie RK, Roth BJ (2006). *http://personalwebs.oakland.edu/~roth/hobbie.htm|Intermediate Physics for Medicine and Biology* (4th ed.). Springer. ISBN 978-0387309422. http://personalwebs.oakland. edu/~roth/hobbie.htm.

External links

- Biophysical Society (http://www.biophysics.org/)
- Educational Resources from Biophysical Society (http://www.biophysics.org/education/resources.htm|)
- The European Biophysical Societies Association (http://www.ebsa.org/)
- The Wellcome Trust Physiome Project (http://www.physiome.ox.ac.uk/) - Links
- Nasif Nahle, Biophysics (http://biocab.org/Biophysics.html)

Biochemistry

Biochemistry is the study of the chemical processes in living organisms. It deals with the structure and function of cellular components such as proteins, carbohydrates, lipids, nucleic acids and other biomolecules.

Although there are a vast number of different biomolecules many are complex and large molecules (called *polymers*) that are composed of similar repeating subunits (called *monomers*). Each class of polymeric biomolecule has a different set of subunit types.[1] For example, a protein is a polymer whose subunits are selected from a set of 20 or more amino acids. Biochemistry studies the chemical properties of important biological molecules, like proteins, in particular the chemistry of enzyme-catalyzed reactions.

The biochemistry of cell metabolism and the endocrine system has been extensively described. Other areas of biochemistry include the genetic code (DNA, RNA), protein synthesis, cell membrane transport, and signal transduction.

Since all known life forms that are still alive today are descended from the same common ancestor, they have generally similar biochemistries.[2] [3] It is unknown whether alternative biochemistries are possible or practical.

History

Originally, it was generally believed that life was not subject to the laws of science the way non-life was. It was thought that only living beings could produce the molecules of life (from other, previously existing biomolecules). Then, in 1828, Friedrich Wöhler published a paper on the synthesis of urea, proving that organic compounds can be created artificially.[4] [5]

The dawn of biochemistry may have been the discovery of the first enzyme, diastase (today called amylase), in 1833 by Anselme Payen. Eduard Buchner contributed the first demonstration of a complex biochemical process outside of a cell in 1896: alcoholic fermentation in cell extracts of yeast. Although the term "biochemistry" seems to have been first used in 1882, it is generally accepted that the formal coinage of biochemistry occurred in 1903 by Carl Neuberg, a German chemist. Previously, this area would have been referred to as physiological chemistry. Since then, biochemistry has advanced, especially since the mid-20th century, with the development of new techniques such as chromatography, X-ray diffraction, dual polarisation interferometry, NMR spectroscopy, radioisotopic labeling, electron microscopy and molecular dynamics simulations. These techniques allowed for the discovery and detailed analysis of many molecules and metabolic pathways of the cell, such as glycolysis and the Krebs cycle (citric acid cycle).

Another significant historic event in biochemistry is the discovery of the gene and its role in the transfer of information in the cell. This part of biochemistry is often called molecular biology. In the 1950s, James D. Watson, Francis Crick, Rosalind Franklin, and Maurice Wilkins were instrumental in solving DNA structure and suggesting its relationship with genetic transfer of information. In 1958, George Beadle and Edward Tatum received the Nobel Prize for work in fungi showing that one gene produces one enzyme. In 1988, Colin Pitchfork was the first person convicted of murder with DNA evidence, which led to growth of forensic science. More recently, Andrew Z. Fire and Craig C. Mello received the 2006 Nobel Prize for discovering the role of RNA interference (RNAi), in the silencing of gene expression
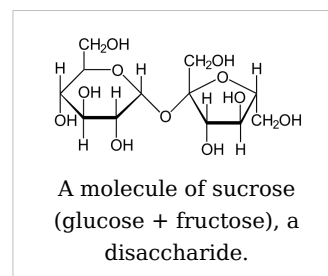
Today, there are three main types of biochemistry. Plant biochemistry involves the study of the biochemistry of autotrophic organisms such as photosynthesis and other plant specific biochemical processes. General biochemistry encompasses both plant and animal biochemistry. Human/medical/medicinal biochemistry focuses on the biochemistry of humans and medical illnesses.
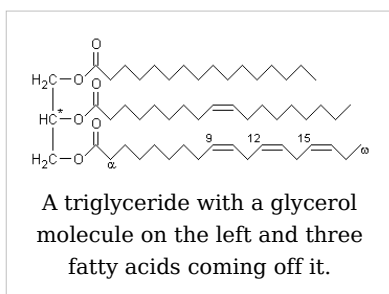
Monomers and Polymers

Monomers and polymers are a structural basis in which the four main macromolecules (Carbohydrates, lipids, proteins, and nucleic acids), or biopolymers, of biochemistry are based on. *Monomers* are smaller micromolecules that are put together to make macromolecules. *Polymers* are those macromolecules that are created when monomers are synthesized together. When they are synthesized, the two molecules undergo a process called dehydration synthesis.

Carbohydrates

Carbohydrates have monomers called monosaccharides. Some of these *monosaccharides* include glucose ($C_6H_{12}O_6$), fructose ($C_6H_{12}O_6$), and deoxyribose ($C_5H_{10}O_4$). When two monosaccharides undergo dehydration synthesis, water is produced, as two hydrogen atoms and one oxygen atom are lost from the two monosaccharides' carboxyl group.
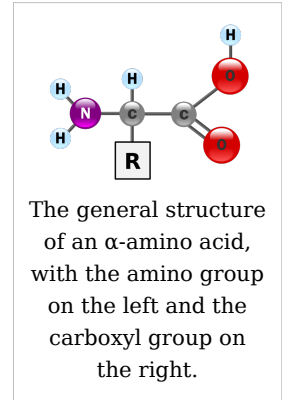

A molecule of sucrose (glucose + fructose), a disaccharide.

Lipids

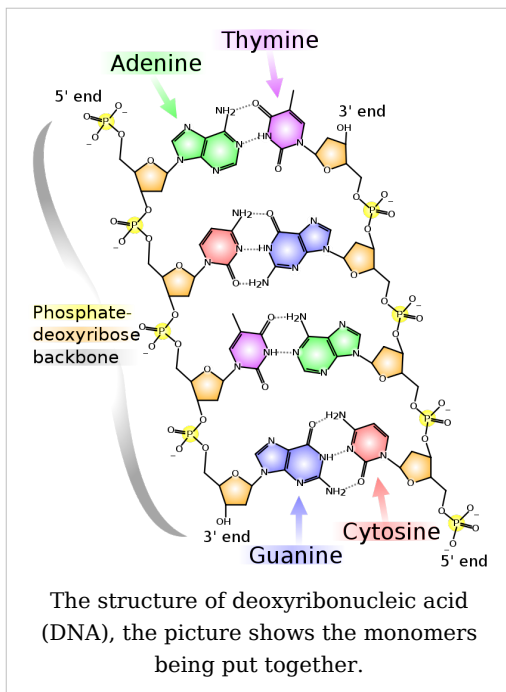A triglyceride with a glycerol molecule on the left and three fatty acids coming off it.

Lipids are usually made up of a molecule of glycerol and other molecules. In triglycerides, or the main lipid, there is one molecule of glycerol, and three fatty acids. Fatty acids are considered the monomer in that case, and could be saturated or unsaturated. Lipids, especially phospholipids, are also used in different pharmaceutical products, either as co-solubilisers e.g. in Parenteral infusions or else as drug carrier components (e.g. in a Liposome or Transfersome).

Proteins

Proteins are large molecules, and have monomers of **amino acids**. There are 20 standard amino acids, and they contain a carboxyl group, an amino group, and an "R" group. The "R" group is what makes each amino acid different. When Amino acids combine, they form a special bond called a peptide bond, and become a ***polypeptide***, or a protein.

The general structure of an α-amino acid, with the amino group on the left and the carboxyl group on the right.

Nucleic Acids

The structure of deoxyribonucleic acid (DNA), the picture shows the monomers being put together.

Nucleic acids are very important in biochemistry, as they are what make up DNA, something all cellular organism use to store their genetic information. The most common nucleic acids are deoxyribonucleic acid and ribonucleic acid. Their monomers are called nucleotides. The most common nucleotides are called adenine, cytosine, guanine, thymine, and uracil. Adenine binds with thymine and uracil, thymine only binds with adenine, and cytosine and guanine can only bind with each other.

Carbohydrates

The function of carbohydrates includes energy storage and providing structure. Sugars are carbohydrates, but not all carbohydrates are sugars. There are more carbohydrates on Earth than any other known type of biomolecule; they are used to store energy and genetic information, as well as play important roles in cell to cell interactions and communications.

Monosaccharides

The simplest type of carbohydrate is a monosaccharide, which among other properties contains carbon, hydrogen, and oxygen, mostly in a ratio of 1:2:1 (generalized formula $C_nH_{2n}O_n$, where n is at least 3). Glucose, one of the most important carbohydrates, is an example of a monosaccharide. So is fructose, the sugar that gives fruits their sweet taste. Some carbohydrates
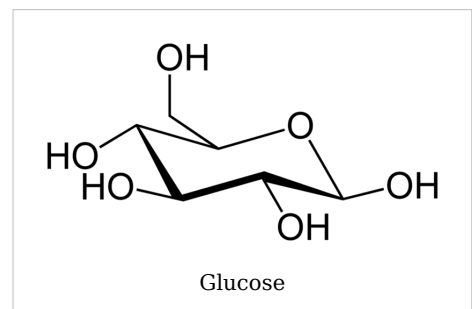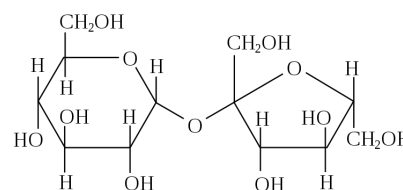

Glucose

(especially after condensation to oligo- and polysaccharides) contain less carbon relative to H and O, which still are present in 2:1 (H:O) ratio. Monosaccharides can be grouped into aldoses (having an aldehyde group at the end of the chain, e. g. glucose) and ketoses (having a keto group in their chain; e. g. fructose). Both aldoses and ketoses occur in an equilibrium between the open-chain forms and (starting with chain lengths of C4) cyclic forms. These are generated by bond formation between one of the hydroxyl groups of the sugar chain with the carbon of the aldehyde or keto group to form a hemiacetal bond. This leads to saturated five-membered (in furanoses) or six-membered (in pyranoses) heterocyclic rings containing one O as heteroatom.

Disaccharides

Two monosaccharides can be joined together using dehydration synthesis, in which a hydrogen atom is removed from the end of one molecule and a hydroxyl group (—OH) is removed from the other; the remaining residues are then attached at the sites from which the atoms were removed. The H—OH or H_2O is then released as a molecule of water, hence the term *dehydration*. The new molecule, consisting of two monosaccharides, is called a *disaccharide* and is conjoined together by a glycosidic or ether bond. The

Sucrose: ordinary table sugar and probably the most familiar carbohydrate.

reverse reaction can also occur, using a molecule of water to split up a disaccharide and break the glycosidic bond; this is termed *hydrolysis*. The most well-known disaccharide is sucrose, ordinary sugar (in scientific contexts, called *table sugar* or *cane sugar* to differentiate it from other sugars). Sucrose consists of a glucose molecule and a fructose molecule joined together. Another important disaccharide is lactose, consisting of a glucose molecule and a galactose molecule. As most humans age, the production of lactase, the enzyme that hydrolyzes lactose back into glucose and galactose, typically decreases. This results in lactase deficiency, also called *lactose intolerance*.

Sugar polymers are characterised by having reducing or non-reducing ends. A reducing end of a carbohydrate is a carbon atom which can be in equilibrium with the open-chain aldehyde or keto form. If the joining of monomers takes place at such a carbon atom, the free hydroxy group of the pyranose or furanose form is exchanged with an OH-side chain of another sugar, yielding a full acetal. This prevents opening of the chain to the aldehyde or keto form and renders the modified residue non-reducing. Lactose contains a reducing end at its glucose moiety, whereas the galactose moiety form a full acetal with the C4-OH group of glucose. Saccharose does not have a reducing end because of full acetal formation between the aldehyde carbon of glucose (C1) and the keto carbon of fructose (C2).

Oligosaccharides and polysaccharides

When a few (around three to six) monosaccharides are joined together, it is called an *oligosaccharide* (*oligo-* meaning "few"). These molecules tend to be used as markers and signals, as well as having some other uses. Many monosaccharides joined together make a polysaccharide. They can be joined together in one long linear chain, or they may be branched. Two of the most common polysaccharides are cellulose and glycogen, both consisting of repeating glucose monomers.

Cellulose as polymer of β-D-glucose
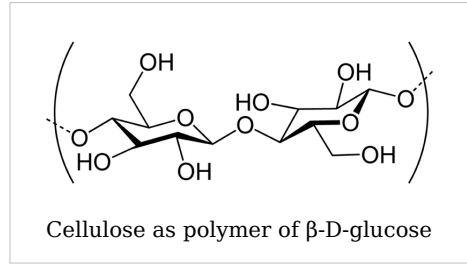
- *Cellulose* is made by plants and is an important structural component of their cell walls. Humans can neither manufacture nor digest it.
- *Glycogen*, on the other hand, is an animal carbohydrate; humans and other animals use it as a form of energy storage.

Use of carbohydrates as an energy source

> *See also carbohydrate metabolism*

Glucose is the major energy source in most life forms. For instance, polysaccharides are broken down into their monomers (glycogen phosphorylase removes glucose residues from glycogen). Disaccharides like lactose or sucrose are cleaved into their two component monosaccharides.

Glycolysis (anaerobic)

Glucose is mainly metabolized by a very important and ancient ten-step pathway called glycolysis, the net result of which is to break down one molecule of glucose into two molecules of pyruvate; this also produces a net two molecules of ATP, the energy currency of cells, along with two reducing equivalents in the form of converting NAD^+ to NADH. This does not require oxygen; if no oxygen is available (or the cell cannot use oxygen), the NAD is restored by converting the pyruvate to lactate (lactic acid) (e. g. in humans) or to ethanol plus carbon dioxide (e. g. in yeast). Other monosaccharides like galactose and fructose can be converted into intermediates of the glycolytic pathway.

Aerobic

In aerobic cells with sufficient oxygen, like most human cells, the pyruvate is further metabolized. It is irreversibly converted to acetyl-CoA, giving off one carbon atom as the waste product carbon dioxide, generating another reducing equivalent as NADH. The two molecules acetyl-CoA (from one molecule of glucose) then enter the citric acid cycle, producing two more molecules of ATP, six more NADH molecules and two reduced (ubi)quinones (via $FADH_2$ as enzyme-bound cofactor), and releasing the remaining carbon atoms as carbon dioxide. The produced NADH and quinol molecules then feed into the enzyme complexes of the respiratory chain, an electron transport system transferring the electrons ultimately to oxygen and conserving the released energy in the form of a proton gradient over a membrane (inner mitochondrial membrane in eukaryotes). Thereby, oxygen is reduced to water and the original electron acceptors NAD^+ and quinone are regenerated. This is why humans breathe in oxygen and breathe out carbon dioxide. The energy released from transferring the electrons from high-energy states in NADH and quinol is conserved

first as proton gradient and converted to ATP via ATP synthase. This generates an additional *28* molecules of ATP (24 from the 8 NADH + 4 from the 2 quinols), totaling to 32 molecules of ATP conserved per degraded glucose (two from glycolysis + two from the citrate cycle). It is clear that using oxygen to completely oxidize glucose provides an organism with far more energy than any oxygen-independent metabolic feature, and this is thought to be the reason why complex life appeared only after Earth's atmosphere accumulated large amounts of oxygen.

Gluconeogenesis

In vertebrates, vigorously contracting skeletal muscles (during weightlifting or sprinting, for example) do not receive enough oxygen to meet the energy demand, and so they shift to anaerobic metabolism, converting glucose to lactate. The liver regenerates the glucose, using a process called gluconeogenesis. This process is not quite the opposite of glycolysis, and actually requires three times the amount of energy gained from glycolysis (six molecules of ATP are used, compared to the two gained in glycolysis). Analogous to the above reactions, the glucose produced can then undergo glycolysis in tissues that need energy, be stored as glycogen (or starch in plants), or be converted to other monosaccharides or joined into di- or oligosaccharides. The combined pathways of glycolysis during exercise, lactate's crossing via the bloodstream to the liver, subsequent gluconeogenesis and release of glucose into the bloodstream is called the Cori cycle.
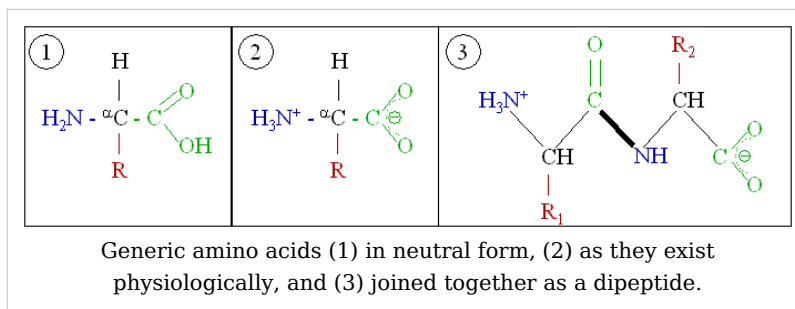
Proteins

Like carbohydrates, some proteins perform largely structural roles. For instance, movements of the proteins actin and myosin ultimately are responsible for the contraction of skeletal muscle. One property many proteins have is that they specifically bind to a certain molecule or class of molecules—they may be *extremely* selective in what they bind. Antibodies are an example of proteins that attach to one specific type of molecule. In fact, the enzyme-linked immunosorbent assay (ELISA), which uses antibodies, is currently one of the most sensitive tests modern medicine uses to detect various biomolecules. Probably the most important proteins, however, are the enzymes. These molecules recognize specific reactant molecules called *substrates*; they then catalyze the reaction between them. By

A schematic of hemoglobin. The red and blue ribbons represent the protein globin; the green structures are the heme groups.

lowering the activation energy, the enzyme speeds up that reaction by a rate of 10^{11} or more: a reaction that would normally take over 3,000 years to complete spontaneously might take less than a second with an enzyme. The enzyme itself is not used up in the process, and is free to catalyze the same reaction with a new set of substrates. Using various modifiers, the activity of the enzyme can be regulated, enabling control of the biochemistry of the cell as a whole.

In essence, proteins are chains of amino acids. An amino acid consists of a carbon atom bound to four groups. One is an amino group, $—NH_2$, and one is a carboxylic acid group, $—COOH$ (although these exist as $—NH_3^+$ and $—COO^-$ under physiologic conditions). The third is a simple hydrogen atom. The fourth is commonly denoted "—R" and is different for
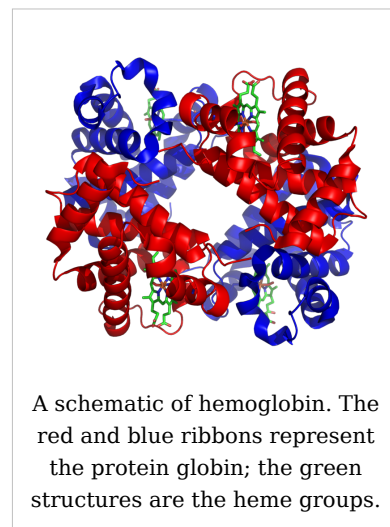
each amino acid. There are twenty standard amino acids. Some of these have functions by themselves or in a modified form; for instance, glutamate functions as an important neurotransmitter.

Amino acids can be joined together via a peptide bond. In this dehydration synthesis, a water molecule is removed and the peptide bond connects the nitrogen of one amino acid's amino group to the carbon of the other's carboxylic acid group. The

Generic amino acids (1) in neutral form, (2) as they exist physiologically, and (3) joined together as a dipeptide.

resulting molecule is called a *dipeptide*, and short stretches of amino acids (usually, fewer than around thirty) are called *peptides* or polypeptides. Longer stretches merit the title *proteins*. As an example, the important blood serum protein albumin contains 585 amino acid residues.

The structure of proteins is traditionally described in a hierarchy of four levels. The primary structure of a protein simply consists of its linear sequence of amino acids; for instance, "alanine-glycine-tryptophan-serine-glutamate-asparagine-glycine-lysine-...".   Secondary structure is concerned with local morphology. Some combinations of amino acids will tend to curl up in a coil called an α-helix or into a sheet called a β-sheet; some α-helixes can be seen in the hemoglobin schematic above. Tertiary structure is the entire three-dimensional shape of the protein. This shape is determined by the sequence of amino acids. In fact, a single change can change the entire structure. The alpha chain of hemoglobin contains 146 amino acid residues; substitution of the glutamate residue at position 6 with a valine residue changes the behavior of hemoglobin so much that it results in sickle-cell disease. Finally quaternary structure is concerned with the structure of a protein with multiple peptide subunits, like hemoglobin with its four subunits. Not all proteins have more than one subunit.

Ingested proteins are usually broken up into single amino acids or dipeptides in the small intestine, and then absorbed. They can then be joined together to make new proteins. Intermediate products of glycolysis, the citric acid cycle, and the pentose phosphate pathway can be used to make all twenty amino acids, and most bacteria and plants possess all the necessary enzymes to synthesize them. Humans and other mammals, however, can only synthesize half of them. They cannot synthesize isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. These are the essential amino acids, since it is essential to ingest them. Mammals do possess the enzymes to synthesize alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, and tyrosine, the nonessential amino acids. While they can synthesize arginine and histidine, they cannot produce it in sufficient amounts for young, growing animals, and so these are often considered essential amino acids.

If the amino group is removed from an amino acid, it leaves behind a carbon skeleton called an α-keto acid. Enzymes called transaminases can easily transfer the amino group from one amino acid (making it an α-keto acid) to another α-keto acid (making it an amino acid). This is important in the biosynthesis of amino acids, as for many of the pathways, intermediates from other biochemical pathways are converted to the α-keto acid skeleton, and then an

amino group is added, often via transamination. The amino acids may then be linked together to make a protein.

A similar process is used to break down proteins. It is first hydrolyzed into its component amino acids. Free ammonia (NH_3), existing as the ammonium ion (NH_4^+) in blood, is toxic to life forms. A suitable method for excreting it must therefore exist. Different strategies have evolved in different animals, depending on the animals' needs. Unicellular organisms, of course, simply release the ammonia into the environment. Similarly, bony fish can release the ammonia into the water where it is quickly diluted. In general, mammals convert the ammonia into urea, via the urea cycle.

Lipids

The term lipid comprises a diverse range of molecules and to some extent is a catchall for relatively water-insoluble or nonpolar compounds of biological origin, including waxes, fatty acids, fatty-acid derived phospholipids, sphingolipids, glycolipids and terpenoids (eg. retinoids and steroids). Some lipids are linear aliphatic molecules, while others have ring structures. Some are aromatic, while others are not. Some are flexible, while others are rigid.

Most lipids have some polar character in addition to being largely nonpolar. Generally, the bulk of their structure is nonpolar or hydrophobic ("water-fearing"), meaning that it does not interact well with polar solvents like water. Another part of their structure is polar or hydrophilic ("water-loving") and will tend to associate with polar solvents like water. This makes them amphiphilic molecules (having both hydrophobic and hydrophilic portions). In the case of cholesterol, the polar group is a mere -OH (hydroxyl or alcohol). In the case of phospholipids, the polar groups are considerably larger and more polar, as described below.

Lipids are an integral part of our daily diet. Most oils and milk products that we use for cooking and eating like butter, cheese, ghee etc, are comprised of fats. Vegetable oils are rich in various polyunsaturated fatty acids (PUFA). Lipid-containing foods undergo digestion within the body and are broken into fatty acids and glycerol, which are the final degradation products of fats and lipids.
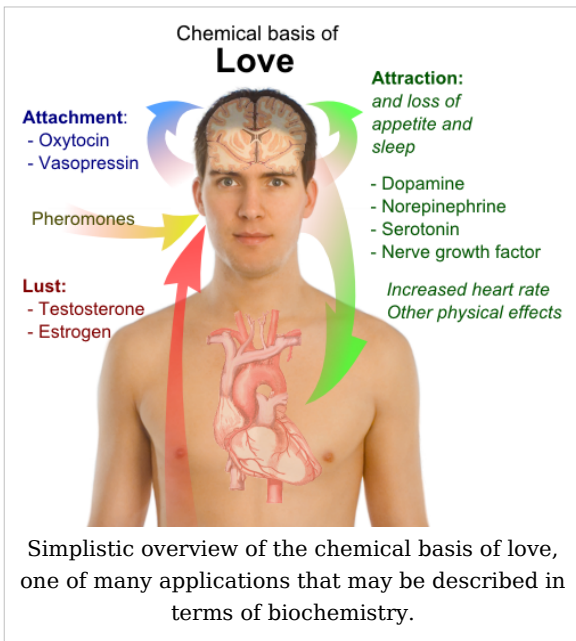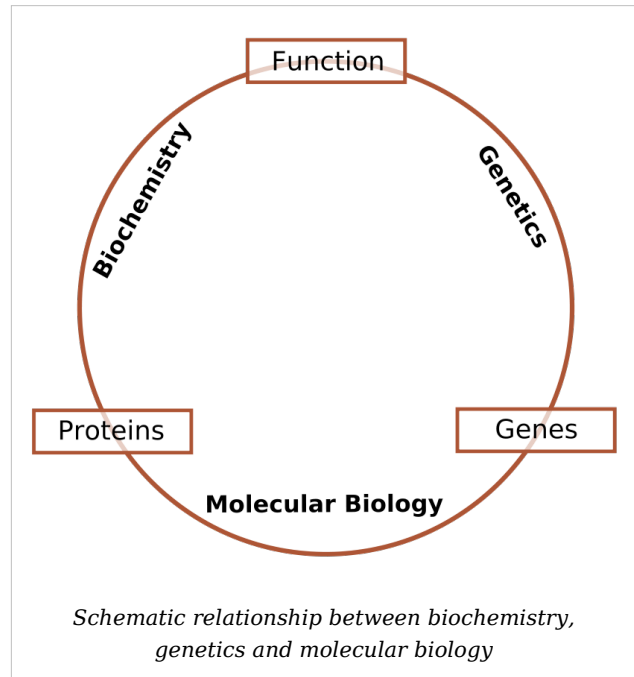
Nucleic acids

A nucleic acid is a complex, high-molecular-weight biochemical macromolecule composed of nucleotide chains that convey genetic information. The most common nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Nucleic acids are found in all living cells and viruses. Aside from the genetic material of the cell, nucleic acids often play a role as second messengers, as well as forming the base molecule for adenosine triphosphate, the primary energy-carrier molecule found in all living organisms.

Nucleic acid, so called because of its prevalence in cellular nuclei, is the generic name of the family of biopolymers. The monomers are called nucleotides, and each consists of three components: a nitrogenous heterocyclic base (either a purine or a pyrimidine), a pentose sugar, and a phosphate group. Different nucleic acid types differ in the specific sugar found in their chain (e.g. DNA or deoxyribonucleic acid contains 2-deoxyriboses). Also, the nitrogenous bases possible in the two nucleic acids are different: adenine, cytosine, and guanine occur in both RNA and DNA, while thymine occurs only in DNA and uracil occurs

in RNA.

Relationship to other "molecular-scale" biological sciences

Researchers in biochemistry use specific techniques native to biochemistry, but increasingly combine these with techniques and ideas from genetics, molecular biology and biophysics. There has never been a hard-line between these disciplines in terms of content and technique, but members of each discipline have in the past been very territorial; today the terms *molecular biology* and *biochemistry* are nearly interchangeable. The following figure is a schematic that depicts one possible view of the relationship between the fields:

Schematic relationship between biochemistry, genetics and molecular biology

Simplistic overview of the chemical basis of love, one of many applications that may be described in terms of biochemistry.

- *Biochemistry* is the study of the chemical substances and vital processes occurring in living organisms. Biochemists focus heavily on the role, function, and structure of biomolecules. The study of the chemistry behind biological processes and the synthesis of biologically active molecules are examples of biochemistry.

- *Genetics* is the study of the effect of genetic differences on organisms. Often this can be inferred by the absence of a normal component (e.g. one gene). The study of "mutants" – organisms which lack one or more functional components with respect to the so-called "wild type" or normal phenotype. Genetic interactions (epistasis) can often confound simple interpretations of such "knock-out" studies.

- *Molecular biology* is the study of molecular underpinnings of the process of replication, transcription and translation of the genetic material. The central dogma of molecular biology where genetic material is transcribed into RNA and then translated into protein, despite being an oversimplified picture of molecular biology, still provides a good starting point for understanding the field. This picture, however, is undergoing revision in light of emerging novel roles for RNA.

- *Chemical Biology* seeks to develop new tools based on small molecules that allow minimal perturbation of biological systems while providing detailed information about their function. Further, chemical biology employs biological systems to create non-natural hybrids between biomolecules and synthetic devices (for example emptied viral capsids that can deliver gene therapy or drug molecules).

See also

Lists

- List of basic biochemistry topics
- List of biochemistry topics
- List of biochemists
- List of biomolecules
- List of geneticists & biochemists
- List of nucleic acid simulation software
- Important publications in biochemistry (biology)
- Important publications in biochemistry (chemistry)

Related topics

- Biological psychiatry
- Biophysics
- Chemical ecology
- Computational biomodeling
- EC number
- Hypothetical types of biochemistry
- International Union of Biochemistry and Molecular Biology
- Metabolome
- Metabolomics
- Molecular biology
- Molecular medicine
- Plant biochemistry
- Structural biology
- Stoichiometry
- Small molecule
- Veterinary

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Further reading

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- Proceedings of National academy of Science of the United States of America (http://www.pnas.org/), ISSN: 1091-6490 (electronic)

External links

- The Virtual Library of Biochemistry and Cell Biology (http://www.biochemweb.org/)
- Biochemistry, 5th ed. (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=stryer.TOC&depth=2) Full text of Berg, Tymoczko, and Stryer, courtesy of NCBI.
- Biochemistry, 2nd ed. (http://www.web.virginia.edu/Heidi/home.htm) Full text of Garrett and Grisham.
- Biochemistry Animation (http://www.1lec.com/Biochemistry/) (Narrated Flash animations.)
- SystemsX.ch - The Swiss Initiative in Systems Biology (http://www.systemsX.ch/)

Major families of biochemicals

Saccharides/Carbohydrates/Glycosides · Amino acids/Peptides/Proteins/Glycoproteins · Lipids/Terpenes/Steroids/Carotenoids · Alkaloids/Nucleobases/Nucleic acids · Cofactors/Flavonoids/Polyketides/Tetrapyrroles

Quantum biocehmistry

Quantum chemistry is a branch of theoretical chemistry, which applies quantum mechanics and quantum field theory to address issues and problems in chemistry. The description of the electronic behavior of atoms and molecules as pertaining to their reactivity is one of the applications of quantum chemistry. Quantum chemistry lies on the border between chemistry and physics, and significant contributions have been made by scientists from both fields. It has a strong and active overlap with the field of atomic physics and molecular physics, as well as physical chemistry.

Quantum chemistry mathematically describes the fundamental behavior of matter at the molecular scale.[1] It is, in principle, possible to describe all chemical systems using this theory. In practice, only the simplest chemical systems may realistically be investigated in purely quantum mechanical terms, and approximations must be made for most practical purposes (e.g., Hartree-Fock, post Hartree-Fock or Density functional theory, see computational chemistry for more details). Hence a detailed understanding of quantum mechanics is not necessary for most chemistry, as the important implications of the theory (principally the orbital approximation) can be understood and applied in simpler terms.

In quantum mechanics the Hamiltonian, or the physical state, of a particle can be expressed as the sum of two operators, one corresponding to kinetic energy and the other to potential energy. The Hamiltonian in the Schrödinger wave equation used in quantum chemistry does not contain terms for the spin of the electron.

Solutions of the Schrödinger equation for the hydrogen atom gives the form of the wave function for atomic orbitals, and the relative energy of the various orbitals. The orbital approximation can be used to understand the other atoms e.g. helium, lithium and carbon.

History

The **history of quantum chemistry** essentially began with the 1838 discovery of cathode rays by Michael Faraday, the 1859 statement of the black body radiation problem by Gustav Kirchhoff, the 1877 suggestion by Ludwig Boltzmann that the energy states of a physical system could be discrete, and the 1900 quantum hypothesis by Max Planck that any energy radiating atomic system can theoretically be divided into a number of discrete energy elements ε such that each of these energy elements is proportional to the frequency ν with which they each individually radiate energy, as defined by the following formula:

$$\epsilon = h\nu$$

where h is a numerical value called Planck's Constant. Then, in 1905, to explain the photoelectric effect (1839), i.e., that shining light on certain materials can function to eject electrons from the material, Albert Einstein postulated, based on Planck's quantum hypothesis, that light itself consists of individual quantum particles, which later came to be called photons (1926). In the years to follow, this theoretical basis slowly began to be applied to chemical structure, reactivity, and bonding.

Electronic structure

The first step in solving a quantum chemical problem is usually solving the Schrödinger equation (or Dirac equation in relativistic quantum chemistry) with the electronic molecular Hamiltonian. This is called determining the **electronic structure** of the molecule. It can be said that the electronic structure of a molecule or crystal implies essentially its chemical properties. An exact solution for the Schrödinger equation can only be obtained for the hydrogen atom. Since all other atomic, or molecular systems, involve the motions of three or more "particles", their Schrödinger equations cannot be solved exactly and so approximate solutions must be sought.

Wave model

The foundation of quantum mechanics and quantum chemistry is the **wave model**, in which the atom is a small, dense, positively charged nucleus surrounded by electrons. Unlike the earlier Bohr model of the atom, however, the wave model describes electrons as "clouds" moving in orbitals, and their positions are represented by probability distributions rather than discrete points. The strength of this model lies in its predictive power. Specifically, it predicts the pattern of chemically similar elements found in the periodic table. The wave model is so named because electrons exhibit properties (such as interference) traditionally associated with waves. See wave-particle duality.

Valence bond

Although the mathematical basis of quantum chemistry had been laid by Schrödinger in 1926, it is generally accepted that the first true calculation in quantum chemistry was that of the German physicists Walter Heitler and Fritz London on the hydrogen (H_2) molecule in 1927. Heitler and London's method was extended by the American theoretical physicist John C. Slater and the American theoretical chemist Linus Pauling to become the **Valence-Bond (VB)** [or **Heitler-London-Slater-Pauling (HLSP)**] method. In this method, attention is primarily devoted to the pairwise interactions between atoms, and this method therefore correlates closely with classical chemists' drawings of bonds.

Molecular orbital

An alternative approach was developed in 1929 by Friedrich Hund and Robert S. Mulliken, in which electrons are described by mathematical functions delocalized over an entire molecule. The **Hund-Mulliken** approach or **molecular orbital (MO) method** is less intuitive to chemists, but has turned out capable of predicting spectroscopic properties better than the VB method. This approach is the conceptional basis of the **Hartree-Fock method** and further post Hartree-Fock methods.

Density functional theory

The **Thomas-Fermi model** was developed independently by Thomas and Fermi in 1927. This was the first attempt to describe many-electron systems on the basis of electronic density instead of wave functions, although it was not very successful in the treatment of entire molecules. The method did provide the basis for what is now known as **density functional theory**. Though this method is less developed than post Hartree-Fock methods, its lower computational requirements allow it to tackle larger polyatomic molecules and even macromolecules, which has made it the most used method in computational chemistry

at present.

Chemical dynamics

A further step can consist of solving the Schrödinger equation with the total molecular Hamiltonian in order to study the motion of molecules. Direct solution of the Schrödinger equation is called *quantum molecular dynamics*, within the semiclassical approximation *semiclassical molecular dynamics*, and within the classical mechanics framework *molecular dynamics (MD)*. Statistical approaches, using for example Monte Carlo methods, are also possible.

Adiabatic chemical dynamics

In **adiabatic dynamics**, interatomic interactions are represented by single scalar potentials called potential energy surfaces. This is the Born-Oppenheimer approximation introduced by Born and Oppenheimer in 1927. Pioneering applications of this in chemistry were performed by Rice and Ramsperger in 1927 and Kassel in 1928, and generalized into the RRKM theory in 1952 by Marcus who took the transition state theory developed by Eyring in 1935 into account. These methods enable simple estimates of unimolecular reaction rates from a few characteristics of the potential surface.

Non-adiabatic chemical dynamics

Non-adiabatic dynamics consists of taking the interaction between several coupled potential energy surface (corresponding to different electronic quantum states of the molecule). The coupling terms are called **vibronic couplings**. The pioneering work in this field was done by Stueckelberg, Landau, and Zener in the 1930s, in their work on what is now known as the Landau-Zener transition. Their formula allows the transition probability between two diabatic potential curves in the neighborhood of an avoided crossing to be calculated.

Quantum chemistry and quantum field theory

The application of quantum field theory (QFT) to chemical systems and theories has become increasingly common in the modern physical sciences. One of the first and most fundamentally explicit appearances of this is seen in the theory of the photomagneton. In this system, plasmas, which are ubiquitous in both physics and chemistry, are studied in order to determine the basic quantization of the underlying bosonic field. However, quantum field theory is of interest in many fields of chemistry, including: nuclear chemistry, astrochemistry, sonochemistry, and quantum hydrodynamics. Field theoretic methods have also been critical in developing the ab initio Effective Hamiltonian theory of semi-empirical pi-electron methods.

See also

- Atomic physics
- Computational chemistry
- Condensed matter physics
- International Academy of Quantum Molecular Science
- Physical chemistry
- Quantum chemistry computer programs
- Quantum electrochemistry
- QMC@Home
- Theoretical physics

Further reading

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- Pauling, L., and Wilson, E. B. *Introduction to Quantum Mechanics with Applications to Chemistry* (Dover Publications) ISBN 0-486-64871-0
- Atkins, P.W. *Physical Chemistry* (Oxford University Press) ISBN 0-19-879285-9
- McWeeny, R. *Coulson's Valence* (Oxford Science Publications) ISBN 0-19-855144-4
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- Bernard Pullman and Alberte Pullman. 1963. *Quantum Biochemistry.*, New York and London: Academic Press.
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External links

- The Sherrill Group - Notes (http://vergil.chemistry.gatech.edu/notes/index.html)
- ChemViz Curriculum Support Resources (http://www.shodor.org/chemviz/)
- Early ideas in the history of quantum chemistry (http://www.quantum-chemistry-history.com/)

Nobel lectures by quantum chemists

- Walter Kohn's Nobel lecture (http://nobelprize.org/chemistry/laureates/1998/kohn-lecture.html)
- Rudolph Marcus' Nobel lecture (http://nobelprize.org/chemistry/laureates/1992/marcus-lecture.html)
- Robert Mulliken's Nobel lecture (http://nobelprize.org/chemistry/laureates/1966/mulliken-lecture.html)
- Linus Pauling's Nobel lecture (http://nobelprize.org/chemistry/laureates/1954/pauling-lecture.html)
- John Pople's Nobel lecture (http://nobelprize.org/chemistry/laureates/1998/pople-lecture.html)

Biophysical Chemistry

The **Max Planck Institute for Biophysical Chemistry (Karl Friedrich Bonhoeffer Institute)** in Göttingen is a research institute of the Max Planck Society. Currently, 730 people work at the Institute, 370 of them are scientists.

As one of the institutes within the Max Planck Society it combines the three classical scientific disciplines – biology, physics and chemistry. Founded in 1971, research in the institute initially focussed on physical and chemical problems. It has since undergone a continuous evolution manifested by an expanding range of core subjects and work areas such as neurobiology, biochemistry and molecular biology.

History

The history of the Institute goes back to the year 1949. At that time, the Max Planck Society established the Max Planck Institute for Physical Chemistry in Göttingen as follow-up of the former Kaiser-Wilhelm Institute for Physical Chemistry in Berlin. Karl Friedrich Bonhoeffer, who already worked at the Kaiser Wilhelm Institute became the founding director of the new institute. He was one of the first researchers who applied physical-chemical methods in biological research and thus combined different disciplines of natural sciences in research.
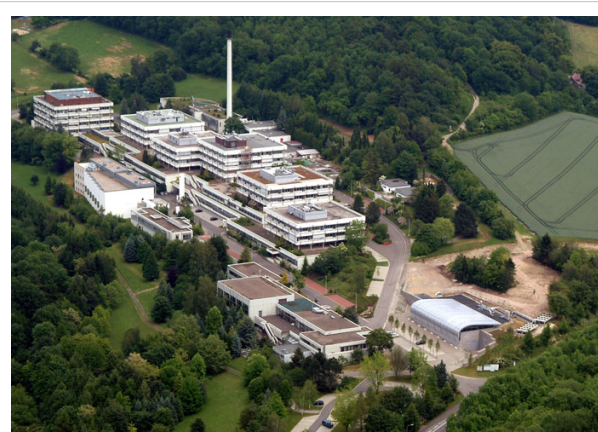
Aerial picture of the Max Planck Institute for biophysical Chemistry, Göttingen (Picture: Jörg Winkler, 2007)

The Max Planck Institute for Biophysical Chemistry was created in 1971 through the merger of Max Planck Institute for Physical Chemistry and for Spectroscopy in Göttingen. This was largely initiated by Nobel Prize winner Manfred Eigen, who was at that time director of the Max Planck Institute for Physical Chemistry. His vision of an interdisciplinary approach to biological research was decisive and the creative impulse for the development of the Institute. To honour Karl Friedrich Bonhoeffer, the new institute

was named after him.

Although the Institute is dedicated to basic research – by virtue of the charter of the Max Planck Society – its policy has been to encourage the transfer of numerous technological innovations to the marketplace. As a consequence, many licensing agreements and start-up firms have arisen from research conducted at the Institute, e. g. Lambda Physik, DeveloGen and Evotec.

The history of the Institute also lists numerous prizes to honor outstanding scientific achievements. In 1967, Manfred Eigen received the Nobel Prize for Chemistry for his unique contributions to the field of rapid reaction kinetics. Two scientists of the Institute, Erwin Neher and Bert Sakmann, shared the Nobel Prize for Physiology or Medicine in 1991, awarded for pioneering single channel recording techniques and applications. Numerous science prizes have been awarded to other directors such as the Gottfried Wilhelm Leibniz Prize (Herbert Jäckle 1986, Fritz Peter Schäfer 1986, Erwin Neher and Bert Sakmann 1986, Peter Gruss 1994, Reinhard Lührmann 1996, Christian Griesinger 1998, Reinhard Jahn 2000, Stefan W. Hell 2008) and the "Deutsche Zukunftspreis" by the Federal President (Peter Gruss and Herbert Jäckle 1999, Stefan Hell 2006). Other prizes awarded to scientists of the Institute are the Louis Jeantet Prize (Peter Gruss 1995, Herbert Jäckle 1999) and the Ernst Jung Prize for Medicine (Klaus Weber 1984, Reinhard Lührmann 2003, Reinhard Jahn 2006).

Furthermore, several junior scientists have been awarded different prizes, among them the renowned BioFuture-Prize (Petra Schwille 1998, Tom Tuschl 1999, Holger Stark 2005).

Departments and Independent Research Groups

The research conducted at the Max Planck Institute for Biophysical Chemistry covers a broad spectrum. Its aim is to understand biophysical and biochemical processes at a fundamental level.

Departments

The Max Planck Institute for Biophysical Chemistry currently encompasses 11 departments:

- **Prof. Gregor Eichele** - *Genes and Behavior*
- **Prof. Dirk Görlich** - *Cellular Logistics*
- **Prof. Christian Griesinger** - *NMR based Structural Biology*
- **Prof. Helmut Grubmüller** - *Theoretical and Computational Biophysics*
- **Prof. Peter Gruss** - *Molecular Cell Biology*
- **Prof. Stefan W. Hell** - *NanoBiophotonics*
- **Prof. Herbert Jäckle** - *Molecular Developmental Biology*
- **Prof. Reinhard Jahn** - *Neurobiology*
- **Prof. Reinhard Lührmann** - *Cellular Biochemistry*
- **Prof. Erwin Neher** - *Membrane Biophysics*
- **Prof. Jürgen Troe** - *Spectroscopy and Photochemical Kinetics*

Research Groups

The Institute is particularly engaged in the support of junior scientists, which is also indicated by the numerous Junior Research Groups hosted here.

- **Dr Donna Arndt-Jovin** - *Structure and Regulation of Chromatin*
- **Dr Adam Lange** - *Solid-state NMR*
- **Dr Marina Bennati** - *Electron Paramagnetic Resonance*
- **Prof. Christof Biebricher** - *RNA Replication*
- **Dr Berend de Groot** - *Computational Biomolecular Dynamics*
- **Dr Dirk Fasshauer** - *Structural Biochemistry*
- **Dr Wolfgang Fischle** - *Chromatin Biochemistry*
- **Dr Stefan Jakobs** - *Mitochondrial Structure and Dynamics*
- **Prof. Michael Kessel** - *Developmental Biology*
- **Prof. Jürgen Klingauf** - *Microscopy of Synaptic Transmission*
- **Dr Martin Kollmar** - *Structural investigations*
- **Dr Manfred Konrad** - *Enzyme Biochemistry*
- **Prof. Ahmed Mansouri** - *Molecular Cell Differentiation*
- **Prof. Dietmar Pörschke** - *Biomolecular Dynamics*
- **Dr. Takeshi Sakaba** - *Biophysics of Synaptic Transmission*
- **Dr. Reinhard Schuh** - *Molecular Organogenesis*
- **Prof. Dirk Schwarzer** - *Reaction Dynamics*
- **Dr Jaokob Sörensen** - *Molecular Mechanismens of Exocytosis*
- **Dr Holger Stark** - *3D Electron Cryo-microscopy*
- **Dr Anastassia Stoykova / Dr. Kamal Chowdhury** - *Molecular Developmental Neurobiology*
- **Prof. Michael Stuke** - *Laser Chemical Processing*
- **Dr Simone Techert** - *Structural Dynamics of (Bio)chemical Systems*
- **Dr Henning Urlaub** - *Bioanalytical Mass Spectrometry*
- **Dr Markus Wahl** - *X-Ray Crystallography*
- **Prof. Peter Jomo Walla** - *Labelfree Biomolecular Analysis and Single-Molecule Detection*
- **Dr Markus Zweckstetter** - *Protein Structure Determination using NMR*

Emeritus Groups

After being retired, directors of the Institute can actively continue their research for a couple of years.

- **Prof. Dieter Gallwitz** - *Molecular Genetics*
- **Prof. Thomas Jovin** - *Laboratory for Cellular Dynamics*
- **Prof. Klaus Weber** - *Biochemistry and Cell Biology*

Former Departments

The Institute has undergone a permanent change in research by closing of departments after their heads being retired and by continuous establishing new departments. Some of the former directors pursue their research even after their Emeritus Group has been expired and can still be contacted at the Institute (*).

- **Prof. Otto D. Creutzfeldt** - *Neurobiology* (1971-1992)
- **Prof. Manfred Eigen (*)** - *Biochemical Kinetics (1971-1995)*
- **Prof. Manfred Kahlweit (*)** - *Kinetics of Phase Transformations* (1971-1996)
- **Prof. Hans Kuhn** - *Molecular Systems* (1971-1984)
- **Prof. Leo de Maeyer (*)** - *Experimental Methods* (1971-1996)
- **Prof. Bert Sakman** - *Cell Physiology* (1985-1988)
- **Prof. Fritz-Peter Schäfer** - *Laser Physics* (1971-1994)
- **Prof. Hans Strehlow** - *Electrochemistry and Reaction Kinetics* (1971-1984)
- **Prof. Albert Weller** - *Spectroscopy* (1971-1990)
- **Prof. Victor P. Whittaker** - *Neurochemistry* (1973-1987)

Biomedizinische NMR Forschungs GmbH

The Institute also accommodates the independent Biomedizinische NMR Forschungs GmbH [1] headed by Jens Frahm, which was founded in 1993. The focus of his team is the development and application of spatially resolved NMR techniques for non-invasive studies of the central nervous system in animals and humans. These innovative approaches allow for unique insights into the structure, metabolism and function of the intact living brain. Jens Frahm and his coworkers invented a rapid acquisition technique for magnetic resonance imaging termed FLASH MRI (fast low angle shot) technique, that allowed for a 100-fold reduction of the measuring times of cross-sectional and three-dimensional images. The FLASH technique led the ground for many modern MRI applications in diagnostic imaging.

Service Groups

Scientific service groups such as *Electron Microscopy* (Dr Dietmar Riedel), *Mass Spectrometry* (Dr Henning Urlaub) and *Innovative Light Microscopy* (Dr Alexander Egner) develop specific and complex methods. The service facilities are available to all scientists of the Institute and provide help and training in terms of sample preparation and data analysis.

An expert *Information Technology group* maintains the very complex and sophisticated network of computational facilities. The *EU Liaison Office* provides support for all phases of the EU grant application procedure. The *Otto Hahn Library* offers more than 80000 journal volumes, in addition to nearly 40000 monographs. Current journal subscriptions include more than 380 titles. Employees in the workshops of the Institute collaborate with the researchers in order to construct special-purpose equipment. Moreover, they continuously seek improved methods for the graphical and photographic reproduction of scientific results. Two child care facilities operated by the *Kinderhaus Göttingen e.V.* take care of children aged 1 to 4 years.

Activities of the Institute

The Institute offers many activities for the public. Besides guided tours for visitors and students from different schools, the Institute arranges public lectures introducing research of different departments and junior research groups. A one-week *Science and Youth* Program operated every year by the City of Göttingen provides students with insights into the laboratories of the Institute. „Open doors" offer the possibility to visit departments and research groups.

Moreover, the Institute offers a special programme, the *Hands-on Laboratory* of the European Initiative for Communicators of Science (EICOS), which invites journalists from all over Europe and Israel to gain a close-up view of research in the laboratories.

Cooperation with the University of Göttingen and other Research Facilities

The **European Neuroscience Institute (ENI)** in Göttingen has existed since 2000 and is dedicated to the support of independent work of Young Investigators in the field of neurosciences. It presently houses three Young Investigator groups working in the fields of neuroendocrinology, neuroplasticity, and cell biophysics. It is jointly funded by the Medical School of Göttingen University and the Max Planck Institutes for Experimental Medicine and for Biophysical Chemistry.

The **DFG Research Center for Molecular Physiology of the Brain (CMPB)** is a research center funded by the German Research Community (DFG) and unites research groups of the Georg August University Göttingen, the Max Planck Society and the German Primate Center in Göttingen. Their research activities focus on molecular processes underlying brain function and the application of new knowledge from these studies in the development of therapies for psychiatric and neurological disorders.

The **Bernstein Center for Computational Neuroscience (BCCN) Göttingen** was established in 2007. In cooperation with research groups from the Max Planck Institute for Dynamics and Self-Organization, the University of Göttingen, the German Primate Center, and the research lab of Otto Bock HealthCare GmbH, research is conducted in joint projects on the adaptivity of the nervous system ranging from the level of single synapses to the level of cognitive processes.

In 2000, two **International Max Planck Research Schools (IMPRS)** were established together with the Georg August University Göttingen, the German Primate Center and the Max Planck Institute for Experimental Medicine: the IMPRS for Molecular Biology and the IMPRS for Neurosciences (in cooperation with the Max Planck Institute for Dynamics and Self-Organization and the ENI Göttingen). Entering with a Bachelor's degree, the students receive a broad theoretical and practical training in the first year that is both intensive and interdisciplinary. Upon successful completion of a qualifying exam by the end of the first year (Master of Science, M.Sc.), the students join one of the participating research groups to begin their doctoral thesis, which is to be submitted within three years (PhD).

External links

- Max Planck Institute for Biophysical Chemistry [2]
- Max Planck Society [3]
- Biomedical NMR Research GmbH [4]
- Eicos [5]
- ENI [6]
- CMPB [7]
- BCCN [8]
- IMPRS for Molecular Biology [9]
- IMPRS for Neurosciences [10]

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[2] http://www.mpibpc.gwdg.de/english/
[3] http://www.mpg.de/english/portal/index.html/
[4] http://www.biomednmr.mpg.de/
[5] http://www.eicos.mpg.de/
[6] http://www.eni.gwdg.de/
[7] http://www.cmpb.uni-goettingen.de/
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Theoretical/Mathematical Biophysics and Related Fields of Theoretical Science]]

Mathematical biology

Mathematical biology is also called **theoretical biology**,[1] and sometimes **biomathematics**. It includes at least four major subfields: *biological mathematical modeling*, *relational biology/complex systems biology (CSB)*, *bioinformatics* and *computational biomodeling/biocomputing*. It is an interdisciplinary academic research field with a wide range of applications in biology, medicine[2] and biotechnology.[3]

Mathematical biology aims at the mathematical representation, treatment and modeling of biological processes, using a variety of applied mathematical techniques and tools. It has both theoretical and practical applications in biological, biomedical and biotechnology research. For example, in cell biology, protein interactions are often represented as "cartoon" models, which, although easy to visualize, do not accurately describe the systems studied. In order to do this, precise mathematical models are required. By describing the systems in a quantitative manner, their behavior can be better simulated, and hence properties can be predicted that might not be evident to the experimenter.

Importance

Applying mathematics to biology has a long history, but only recently has there been an explosion of interest in the field. Some reasons for this include:

- the explosion of data-rich information sets, due to the genomics revolution, which are difficult to understand without the use of analytical tools,
- recent development of mathematical tools such as chaos theory to help understand complex, nonlinear mechanisms in biology,
- an increase in computing power which enables calculations and simulations to be performed that were not previously possible, and
- an increasing interest in in silico experimentation due to ethical considerations, risk, unreliability and other complications involved in human and animal research.

For use of basic arithmetics in biology, see relevant topic, such as Serial dilution.

Areas of research

Several areas of specialized research in mathematical and theoretical biology[4] [5] [6] [7] [8] [9] as well as external links to related projects in various universities are concisely presented in the following subsections, including also a large number of appropriate validating references from a list of several thousands of published authors contributing to this field. Many of the included examples are characterised by highly complex, nonlinear, and supercomplex mechanisms, as it is being increasingly recognised that the result of such

interactions may only be understood through a combination of mathematical, logical, physical/chemical, molecular and computational models. Due to the wide diversity of specific knowledge involved, biomathematical research is often done in collaboration between mathematicians, biomathematicians, theoretical biologists, physicists, biophysicists, biochemists, bioengineers, engineers, biologists, physiologists, research physicians, biomedical researchers,oncologists, molecular biologists, geneticists, embryologists, zoologists, chemists, etc.

Computer models and automata theory

A monograph on this topic summarizes an extensive amount of published research in this area up to 1987,[10] including subsections in the following areas: computer modeling in biology and medicine, arterial system models, neuron models, biochemical and oscillation networks, quantum automata [11], quantum computers in molecular biology and genetics, cancer modelling, neural nets, genetic networks, abstract relational biology, metabolic-replication systems, category theory[12] applications in biology and medicine,[13] automata theory,cellular automata, tessallation models[14] [15] and complete self-reproduction [16], chaotic systems in organisms, relational biology and organismic theories.[17] [18] This published report also includes 390 references to peer-reviewed articles by a large number of authors.[19] [20] [21]

Modeling cell and molecular biology

This area has received a boost due to the growing importance of molecular biology.[22]

- Mechanics of biological tissues[23]
- Theoretical enzymology and enzyme kinetics
- Cancer modelling and simulation [24] [25]
- Modelling the movement of interacting cell populations[26]
- Mathematical modelling of scar tissue formation[27]
- Mathematical modelling of intracellular dynamics[28]
- Mathematical modelling of the cell cycle[29]

Modelling physiological systems

- Modelling of arterial disease [30]
- Multi-scale modelling of the heart [31]

Molecular set theory

Molecular set theory was introduced by Anthony Bartholomay, and its applications were developed in mathematical biology and especially in Mathematical Medicine.[32] Molecular set theory (MST) is a mathematical formulation of the wide-sense chemical kinetics of biomolecular reactions in terms of sets of molecules and their chemical transformations represented by set-theoretical mappings between molecular sets. In a more general sense, MST is the theory of molecular categories defined as categories of molecular sets and their chemical transformations represented as set-theoretical mappings of molecular sets. The theory has also contributed to biostatistics and the formulation of clinical biochemistry problems in mathematical formulations of pathological, biochemical changes of interest to Physiology, Clinical Biochemistry and Medicine.[33] [34]

Population dynamics

Population dynamics has traditionally been the dominant field of mathematical biology. Work in this area dates back to the 19th century. The Lotka–Volterra predator-prey equations are a famous example. In the past 30 years, population dynamics has been complemented by evolutionary game theory, developed first by John Maynard Smith. Under these dynamics, evolutionary biology concepts may take a deterministic mathematical form. Population dynamics overlap with another active area of research in mathematical biology: mathematical epidemiology, the study of infectious disease affecting populations. Various models of viral spread have been proposed and analyzed, and provide important results that may be applied to health policy decisions.

Mathematical methods

A model of a biological system is converted into a system of equations, although the word 'model' is often used synonymously with the system of corresponding equations. The solution of the equations, by either analytical or numerical means, describes how the biological system behaves either over time or at equilibrium. There are many different types of equations and the type of behavior that can occur is dependent on both the model and the equations used. The model often makes assumptions about the system. The equations may also make assumptions about the nature of what may occur.

Mathematical biophysics

The earlier stages of mathematical biology were dominated by mathematical biophysics, described as the application of mathematics in biophysics, often involving specific physical/mathematical models of biosystems and their components or compartments.

The following is a list of mathematical descriptions and their assumptions.

Deterministic processes (dynamical systems)

A fixed mapping between an initial state and a final state. Starting from an initial condition and moving forward in time, a deterministic process will always generate the same trajectory and no two trajectories cross in state space.

- Difference equations – discrete time, continuous state space.
- Ordinary differential equations – continuous time, continuous state space, no spatial derivatives. *See also:* Numerical ordinary differential equations.
- Partial differential equations – continuous time, continuous state space, spatial derivatives. *See also:* Numerical partial differential equations.
- Maps – discrete time, continuous state space.

Stochastic processes (random dynamical systems)

A random mapping between an initial state and a final state, making the state of the system a random variable with a corresponding probability distribution.

- Non-Markovian processes – generalized master equation – continuous time with memory of past events, discrete state space, waiting times of events (or transitions between states) discretely occur and have a generalized probability distribution.
- Jump Markov process – master equation – continuous time with no memory of past events, discrete state space, waiting times between events discretely occur and are exponentially distributed. *See also:* Monte Carlo method for numerical simulation methods, specifically continuous-time Monte Carlo which is also called kinetic Monte

Carlo or the stochastic simulation algorithm.
- Continuous Markov process – stochastic differential equations or a Fokker-Planck equation – continuous time, continuous state space, events occur continuously according to a random Wiener process.

Spatial modelling

One classic work in this area is Alan Turing's paper on morphogenesis entitled *The Chemical Basis of Morphogenesis*, published in 1952 in the Philosophical Transactions of the Royal Society.

- Travelling waves in a wound-healing assay[35]
- Swarming behaviour[36]
- A mechanochemical theory of morphogenesis[37]
- Biological pattern formation[38]
- Spatial distribution modeling using plot samples[39]

Phylogenetics

Phylogenetics is an area of mathematical biology that deals with the reconstruction and analysis of phylogenetic (evolutionary) trees and networks based on inherited characteristics. The main mathematical concepts are trees, X-trees and maximum parsimony trees.

Model example: the cell cycle

The eukaryotic cell cycle is very complex and is one of the most studied topics, since its misregulation leads to cancers. It is possibly a good example of a mathematical model as it deals with simple calculus but gives valid results. Two research groups [40] [41] have produced several models of the cell cycle simulating several organisms. They have recently produced a generic eukaryotic cell cycle model which can represent a particular eukaryote depending on the values of the parameters, demonstrating that the idiosyncrasies of the individual cell cycles are due to different protein concentrations and affinities, while the underlying mechanisms are conserved (Csikasz-Nagy et al., 2006).

By means of a system of ordinary differential equations these models show the change in time (dynamical system) of the protein inside a single typical cell; this type of model is called a deterministic process (whereas a model describing a statistical distribution of protein concentrations in a population of cells is called a stochastic process).

To obtain these equations an iterative series of steps must be done: first the several models and observations are combined to form a consensus diagram and the appropriate kinetic laws are chosen to write the differential equations, such as rate kinetics for stoichiometric reactions, Michaelis-Menten kinetics for enzyme substrate reactions and Goldbeter–Koshland kinetics for ultrasensitive transcription factors, afterwards the parameters of the equations (rate constants, enzyme efficiency coefficients and Micheleis constants) must be fitted to match observations; when they cannot be fitted the kinetic equation is revised and when that is not possible the wiring diagram is modified. The parameters are fitted and validated using observations of both wild type and mutants, such as protein half-life and cell size.

In order to fit the parameters the differential equations need to be studied. This can be done either by simulation or by analysis.

In a simulation, given a starting vector (list of the values of the variables), the progression

of the system is calculated by solving the equations at each time-frame in small increments.

In analysis, the proprieties of the equations are used to investigate the behavior of the system depending of the values of the parameters and variables. A system of differential equations can be represented as a vector field, where each vector described the change (in concentration of two or more protein) determining where and how

fast the trajectory (simulation) is heading. Vector fields can have several special points: a stable point, called a sink, that attracts in all directions (forcing the concentrations to be at a certain value), an unstable point, either a source or a saddle point which repels (forcing the concentrations to change away from a certain value), and a limit cycle, a closed trajectory towards which several trajectories spiral towards (making the concentrations oscillate).

A better representation which can handle the large number of variables and parameters is called a bifurcation diagram(Bifurcation theory): the presence of these special steady-state points at certain values of a parameter (e.g. mass) is represented by a point and once the parameter passes a certain value, a qualitative change occurs, called a bifurcation, in which the nature of the space changes, with profound consequences for the protein concentrations: the cell cycle has phases (partially corresponding to G1 and G2) in which mass, via a stable point, controls cyclin levels, and phases (S and M phases) in which the concentrations change independently, but once the phase has changed at a bifurcation event (Cell cycle checkpoint), the system cannot go back to the previous levels since at the current mass the vector field is profoundly different and the mass cannot be reversed back through the bifurcation event, making a checkpoint irreversible. In particular the S and M checkpoints are regulated by means of special bifurcations called a Hopf bifurcation and an infinite period bifurcation.
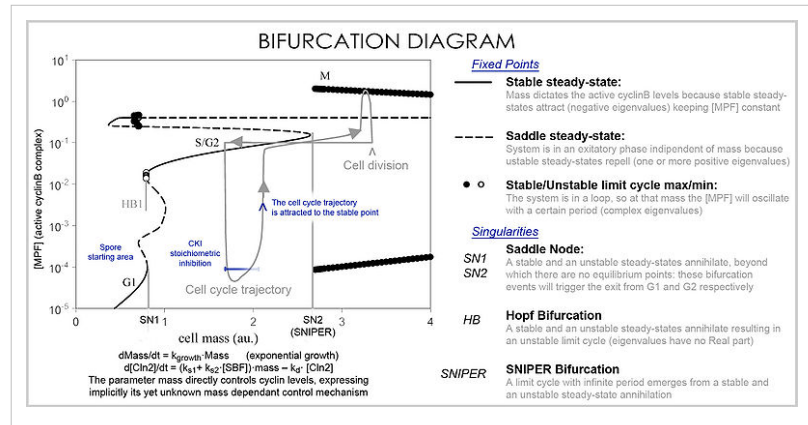
Mathematical/theoretical biologists

- Pere Alberch
- Anthony F. Bartholomay
- J. T. Bonner
- Jack Cowan
- Gerd B. Müller
- Walter M. Elsasser
- Claus Emmeche
- Andree Ehresmann
- Marc Feldman
- Ronald A. Fisher
- Brian Goodwin
- Bryan Grenfell

- J. B. S. Haldane
- William D. Hamilton
- Lionel G. Harrison
- Michael Hassell
- Sven Erik Jørgensen
- George Karreman
- Stuart Kauffman
- Kalevi Kull
- Herbert D. Landahl
- Richard Lewontin
- Humberto Maturana
- Robert May
- John Maynard Smith
- Howard Pattee
- George R. Price
- Erik Rauch
- Nicolas Rashevsky
- Ronald Brown (mathematician)
- Johannes Reinke
- Robert Rosen
- Rene Thom
- Jakob von Uexküll
- Robert Ulanowicz
- Francisco Varela
- C. H. Waddington
- Arthur Winfree
- Lewis Wolpert
- Sewall Wright
- Christopher Zeeman

Mathematical, theoretical and computational biophysicists

- Nicolas Rashevsky
- Ludwig von Bertalanffy
- Francis Crick
- Manfred Eigen
- Walter Elsasser
- Herbert Frohlich, FRS
- Francois Jacob
- Martin Karplus
- George Karreman
- Herbert D. Landahl
- Ilya, Viscount Prigogine
- SirJohn Randall
- James D. Murray
- Bernard Pullman
- Alberte Pullman
- Erwin Schrodinger

- Klaus Schulten
- Peter Schuster
- Zeno Simon
- D'Arcy Thompson
- Murray Gell-Mann

See also

- Abstract relational biology [42][43] [44]
- Biocybernetics
- Bioinformatics
- Biologically inspired computing
- Biostatistics
- Cellular automata[45]
- Coalescent theory
- Complex systems biology[46] [47] [48]
- Computational biology
- Dynamical systems in biology[49] [50] [51] [52] [53] [54]
- Epidemiology
- Evolution theories and Population Genetics

  - Population genetics models
  - Molecular evolution theories
- Ewens's sampling formula
- Excitable medium
- Mathematical models

  - Molecular modelling
  - Software for molecular modeling
  - Metabolic-replication systems [55][56]
  - Models of Growth and Form
  - Neighbour-sensing model
- Morphometrics
- Organismic systems (OS) [57][58]
- Organismic supercategories [57][59] [60]
- Population dynamics of fisheries
- Protein folding, also blue Gene and folding@home
- Quantum computers
- Quantum genetics
- Relational biology [61]
- Self-reproduction[62] (also called self-replication in a more general context).
- Computational gene models
- Systems biology[63]
- Theoretical biology[64]
- Topological models of morphogenesis

  - DNA topology
  - DNA sequencing theory

    For use of basic arithmetics in biology, see relevant topic, such as Serial dilution.
- Biographies

- Charles Darwin
- D'Arcy Thompson
- Joseph Fourier
- Charles S. Peskin
- Nicolas Rashevsky [65]
- Robert Rosen
- Rosalind Franklin
- Francis Crick
- René Thom
- Vito Volterra

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- A list of references for applications of category theory in relational biology[72] .
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External links

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- Complexity Discussion Group (http://www.complex.vcu.edu/)
- Integrative cancer biology modeling and Complex systems biology (http://fs512.fshn.uiuc.edu/ComplexSystemsBiology.htm)
- UCLA Biocybernetics Laboratory (http://biocyb.cs.ucla.edu/research.html)
- TUCS Computational Biomodelling Laboratory (http://www.tucs.fi/research/labs/combio.php)
- Nagoya University Division of Biomodeling (http://www.agr.nagoya-u.ac.jp/english/e3senko-1.html)
- Technische Universiteit Biomodeling and Informatics (http://www.bmi2.bmt.tue.nl/Biomedinf/)
- BioCybernetics Wiki, a vertical wiki on biomedical cybernetics and systems biology (http://wiki.biological-cybernetics.de)
- Society for Mathematical Biology (http://www.smb.org/)
- Bulletin of Mathematical Biology (http://www.springerlink.com/content/119979/)
- European Society for Mathematical and Theoretical Biology (http://www.esmtb.org/)
- Journal of Mathematical Biology (http://www.springerlink.com/content/100436/)
- Biomathematics Research Centre at University of Canterbury (http://www.math.canterbury.ac.nz/bio/)
- Centre for Mathematical Biology at Oxford University (http://www.maths.ox.ac.uk/cmb/)

- Mathematical Biology at the National Institute for Medical Research (http://mathbio. nimr.mrc.ac.uk/)
- Institute for Medical BioMathematics (http://www.imbm.org/)
- *Mathematical Biology Systems of Differential Equations* (http://eqworld.ipmnet.ru/en/ solutions/syspde/spde-toc2.pdf) from EqWorld: The World of Mathematical Equations
- Systems Biology Workbench - a set of tools for modelling biochemical networks (http:// sbw.kgi.edu)
- The Collection of Biostatistics Research Archive (http://www.biostatsresearch.com/ repository/)
- Statistical Applications in Genetics and Molecular Biology (http://www.bepress.com/ sagmb/)
- The International Journal of Biostatistics (http://www.bepress.com/ijb/)
- Theoretical Modeling of Cellular Physiology at Ecole Normale Superieure, Paris (http:// www.biologie.ens.fr/bcsmcbs/)

Theoretical biology

Theoretical biology is a field of academic study and research that involves the use of models and theories in biology.

Many separate areas of biology fall under the concept of theoretical biology, according to the way they are studied. Some of these areas include: animal behaviour (ethology), biomechanics, biorhythms, cell biology, complexity of biological systems, ecology, enzyme kinetics, evolutionary biology, genetics, immunology, membrane transport, microbiology, molecular structures, morphogenesis, physiological mechanisms, systems biology and the origin of life. Neurobiology is an example of a subdiscipline of biology which already has a theoretical version of its own, theoretical or computational neuroscience.

The ultimate goal of the theoretical biologist is to explain the biological world using mainly mathematical and computational tools. Though it is ultimately based on observations and experimental results, the theoretical biologist's product is a model or theory, and it is this that chiefly distinguishes the theoretical biologist from other biologists.

Theoretical biologists

- Pere Alberch
- Anthony F. Bartholomay
- Ervin Bauer
- Ludwig von Bertalanffy
- Jan Charles Biro
- J. T. Bonner
- Jack Cowan
- Francis Crick
- Gerd B. Müller
- Walter M. Elsasser
- Claus Emmeche
- Andree Ehresmann
- Marc Feldman

- Ronald A. Fisher
- Brian Goodwin
- Bryan Grenfell
- J. B. S. Haldane
- William D. Hamilton
- Lionel G. Harrison
- Michael Hassell
- Sven Erik Jørgensen
- George Karreman
- Stuart Kauffman
- Kalevi Kull
- Herbert D. Landahl
- Richard Lewontin
- Humberto Maturana
- Robert May
- John Maynard Smith
- James D. Murray
- Howard Pattee
- George R. Price
- Erik Rauch
- Nicolas Rashevsky
- Ronald Brown (mathematician)
- Johannes Reinke
- Robert Rosen
- Peter Schuster
- Rene Thom
- D'Arcy Thompson
- Jakob von Uexküll
- Robert Ulanowicz
- Francisco Varela
- C. H. Waddington
- Arthur Winfree
- Lewis Wolpert
- Sewall Wright
- Christopher Zeeman

See also

- Journal of Theoretical Biology
- Bioinformatics
- Biosemiotics
- Mathematical biology
- Theoretical ecology
- Artificial life

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External links

- Theory of Biological Anthropology (Documents No. 9 and 10 in English) [1]
- Drawing the Line Between Theoretical and Basic Biology (a forum article by Isidro T. Savillo) [2]

Related Journals

- Acta Biotheoretica [3]
- Bioinformatics [4]
- Biological Theory [5]
- BioSystems [6]
- Bulletin of Mathematical Biology [7]
- Ecological Modelling [8]
- Journal of Mathematical Biology [9]
- Journal of Theoretical Biology [10]
- Journal of the Royal Society Interface [11]
- Mathematical Biosciences [12]
- Medical Hypotheses [13]
- Rivista di Biologia-Biology Forum [14]
- Theoretical and Applied Genetics [15]
- Theoretical Biology and Medical Modelling [16]
- Theoretical Population Biology [17]
- Theory in Biosciences [18] (formerly: Biologisches Zentralblatt)

Related societies

- American Mathematical Society [19]
- British Society of Developmental Biology [20]
- European Mathematical Society [21]
- ESMTB: European Society for Mathematical and Theoretical Biology [22]
- The International Biometric Society [23]
- International Society for Ecological Modelling [24]
- The Israeli Society for Theoretical and Mathematical Biology [25]
- London Mathematical Society [26]
- Société Francophone de Biologie Théorique [27]
- Society for Industrial and Applied Mathematics [28]
- Society for Mathematical Biology [29]
- International Society for Biosemiotic Studies [30]

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[5] http://www.mitpressjournals.org/loi/biot/
[6] http://www.elsevier.com/locate/biosystems
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[16] http://www.tbiomed.com/
[17] http://www.elsevier.com/locate/issn/00405809
[18] http://www.elsevier.com/wps/product/cws_home/701802
[19] http://www.ams.org/
[20] http://www.dundee.ac.uk/lifesciences/BSDB/
[21] http://www.maths.soton.ac.uk/EMIS
[22] http://www.esmtb.org/
[23] http://www.tibs.org/
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[26] http://www.lms.ac.uk/
[27] http://www.necker.fr/sfbt/
[28] http://www.siam.org/
[29] http://www.smb.org/
[30] http://www.biosemiotics.org/

Complex Systems Biology

Systems biology is a biology-based inter-disciplinary study field that focuses on the systematic study of complex interactions in biological systems, thus using a new perspective (holism instead of reduction) to study them. Particularly from year 2000 onwards, the term is used widely in the biosciences, and in a variety of contexts. Because the scientific method has been used primarily toward reductionism, one of the goals

Example of systems biology research.

of systems biology is to discover new emergent properties that may arise from the systemic view used by this discipline in order to understand better the entirety of processes that happen in a biological system.
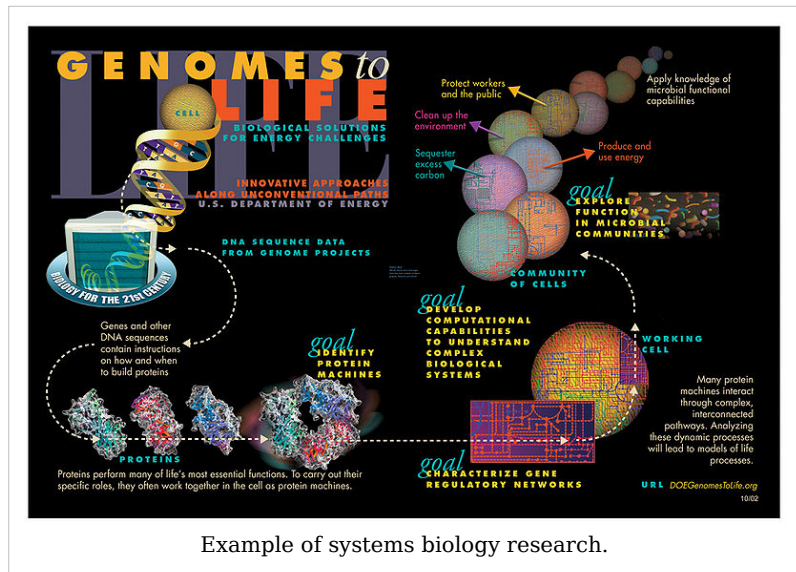
Overview

Systems biology can be considered from a number of different aspects:

- Some sources discuss systems biology as a **field of study**, particularly, the study of the interactions between the components of *biological systems*, and how these interactions give rise to the function and behavior of that system (for example, the enzymes and metabolites in a metabolic pathway).[1] [2]

- Other sources consider systems biology as a **paradigm**, usually defined in antithesis to the so-called reductionist paradigm, although fully consistent with the scientific method. The distinction between the two paradigms is referred to in these quotations:

  "*The reductionist approach has successfully identified most of the components and many of the interactions but, unfortunately, offers no convincing concepts or methods to understand how system properties emerge...the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures, multiple components simultaneously and by rigorous data integration with mathematical models*" Science[3]

  "*Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different....It means changing our philosophy, in the full sense of the term*" Denis Noble[4]

- Still other sources view systems biology in terms of the **operational protocols used for performing research**, namely a cycle composed of theory, analytic or computational modelling to propose specific testable hypotheses about a biological system, experimental validation, and then using the newly acquired quantitative description of

cells or cell processes to refine the computational model or theory.[5] [6] Since the objective is a model of the interactions in a system, the experimental techniques that most suit systems biology are those that are system-wide and attempt to be as complete as possible. Therefore, transcriptomics, metabolomics, proteomics and high-throughput techniques are used to collect quantitative data for the construction and validation of models.

- Engineers consider systems biology as the application of dynamical systems theory to molecular biology.

- Finally, some sources see it as a **socioscientific phenomenon** defined by the strategy of pursuing integration of complex data about the interactions in biological systems from diverse experimental sources using interdisciplinary tools and personnel.

This variety of viewpoints is illustrative of the fact that systems biology refers to a cluster of peripherally overlapping concepts rather than a single well-delineated field. However the term has widespread currency and popularity as of 2007, with chairs and institutes of systems biology proliferating worldwide (Such as the Institute for Systems Biology).

History

Systems biology finds its roots in:

- the quantitative modelling of enzyme kinetics, a discipline that flourished between 1900 and 1970,
- the simulations developed to study neurophysiology, and
- control theory and cybernetics.

One of the theorists who can be seen as a precursor of systems biology is Ludwig von Bertalanffy with his general systems theory, and his book titled "General Systems Theory in Physics and Biology" was published in 1950. One of the first numerical simulations in biology was published in 1952 by the British neurophysiologists and Nobel prize winners Alan Lloyd Hodgkin and Andrew Fielding Huxley, who constructed a mathematical model that explained the action potential propagating along the axon of a neuronal cell.[7] Their model described a cellular function emerging from the interaction between two different molecular components, a potassium and a sodium channels, and can therefore be seen as the beginning of computational systems biology.[8] In 1960, Denis Noble developed the first computer model of the heart pacemaker.[9]

The formal study of systems biology, as a distinct discipline, was launched by systems theorist Mihajlo Mesarovic in 1966 with an international symposium at the Case Institute of Technology in Cleveland, Ohio entitled "Systems Theory and Biology."[10] [11]

The 1960s and 1970s saw the development of several approaches to study complex molecular systems, such as the Metabolic Control Analysis and the biochemical systems theory. The successes of molecular biology throughout the 1980s, coupled with a skepticism toward theoretical biology, that then promised more than it achieved, caused the quantitative modelling of biological processes to become a somewhat minor field.

Since the established of the systems theory, the terms of systems ecology (Van Dyne GM.1966), systems physiology (Sagawa K.1973), system psychology (Edward B. Titchener 1992), system biomedicine (Kamada T.1992), systems biology (Zieglgansberger W, Tolle TR.1993) can be searched from the PubMed of NIH, USA. The concept and model of system medicine (Zeng BJ.) was published at the first national conference on Chinese Traditional

Medicince and west medicine in Guangzhou, China 1992. During 1990s years, Zeng B.J. (Institute of Microbiology, CAS, Beijing) established the concepts of "systems genetics" and "system biological engineering" for the third wave of genetics and engineering of artificial biosystems, and created the genbrain biosystem network of the (world) associates for biosystem science and engineering in Jan. 1999.

However the birth of functional genomics in the 1990s meant that large quantities of high quality data became available, while the computing power exploded, making more realistic models possible. In 1997, the group of Masaru Tomita published the first quantitative model of the metabolism of a whole (hypothetical) cell.

Around the year 2000, when Institutes of Systems Biology were established in Seattle and Tokyo, systems biology emerged as a movement in its own right, spurred on by the completion of various genome projects, the large increase in data from the omics (e.g. genomics and proteomics) and the accompanying advances in high-throughput experiments and bioinformatics. Since then, various research institutes dedicated to systems biology have been developed. As of summer 2006, due to a shortage of people in systems biology[12] several doctoral training centres in systems biology have been established in many parts of the world.

Techniques associated with systems biology

According to the interpretation of System Biology as the ability to obtain, integrate and analyze complex data from multiple experimental sources using interdisciplinary tools, some typical technology platforms are:

Overview of signal transduction pathways

- Transcriptomics: whole cell or tissue gene expression measurements by DNA microarrays or serial analysis of gene expression
- Proteomics: complete identification of proteins and protein expression patterns of a cell or tissue through two-dimensional gel electrophoresis and mass spectrometry or multi-dimensional protein identification techniques (advanced HPLC systems coupled with mass spectrometry). Sub disciplines include phosphoproteomics, glycoproteomics and other methods to detect chemically modified proteins.
- Metabolomics: identification and measurement of all small-molecules metabolites within a cell or tissue
- Glycomics: identification of the entirety of all carbohydrates in a cell or tissue.
- Lipidomics: identification of the entirety of all lipids in a cell or tissue.

In addition to the identification and quantification of the above given molecules further techniques analyze the dynamics and interactions within a cell. This includes:
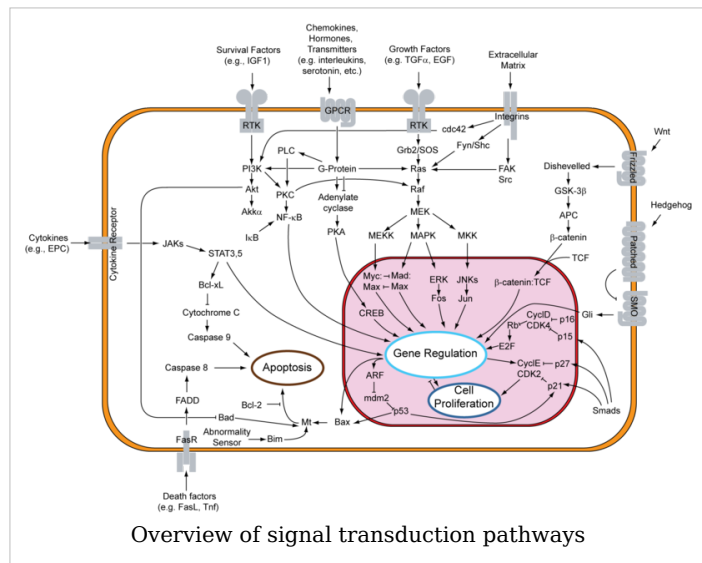
- Interactomics which is used mostly in the context of protein-protein interaction but in theory encompasses interactions between all molecules within a cell,
- Fluxomics, which deals with the dynamic changes of molecules within a cell over time,
- Biomics: systems analysis of the biome.

The investigations are frequently combined with large scale perturbation methods, including gene-based (RNAi, mis-expression of wild type and mutant genes) and chemical approaches using small molecule libraries. Robots and automated sensors enable such large-scale experimentation and data acquisition. These technologies are still emerging and many face problems that the larger the quantity of data produced, the lower the quality. A wide variety of quantitative scientists (computational biologists, statisticians, mathematicians, computer scientists, engineers, and physicists) are working to improve the quality of these approaches and to create, refine, and retest the models to accurately reflect observations.

The investigations of a single level of biological organization (such as those listed above) are usually referred to as Systematic Systems Biology. Other areas of Systems Biology includes Integrative Systems Biology, which seeks to integrate different types of information to advance the understanding the biological whole, and Dynamic Systems Biology, which aims to uncover how the biological whole changes over time (during evolution, for example, the onset of disease or in response to a perturbation). Functional Genomics may also be considered a sub-field of Systems Biology.

The systems biology approach often involves the development of mechanistic models, such as the reconstruction of dynamic systems from the quantitative properties of their elementary building blocks.[13] [14] For instance, a cellular network can be modelled mathematically using methods coming from chemical kinetics and control theory. Due to the large number of parameters, variables and constraints in cellular networks, numerical and computational techniques are often used. Other aspects of computer science and informatics are also used in systems biology. These include new forms of computational model, such as the use of process calculi to model biological processes, the integration of information from the literature, using techniques of information extraction and text mining, the development of online databases and repositories for sharing data and models (such as BioModels Database), approaches to database integration and software interoperability via loose coupling of software, websites and databases[15] and the development of syntactically and semantically sound ways of representing biological models, such as the Systems Biology Markup Language (SBML).

See also

Related fields

- Complex systems biology
- Complex systems
- Complex systems biology
- Bioinformatics
- Biological network inference
- Biological systems engineering
- Biomedical cybernetics
- Biostatistics
- Theoretical Biophysics
- Relational Biology
- Translational Research
- Computational biology
- Computational systems biology

- Scotobiology
- Synthetic biology
- Systems biology modeling
- Systems ecology
- Systems immunology

Related terms

- Life
- Artificial life
- Gene regulatory network
- Metabolic network modelling
- Living systems theory
- Network Theory of Aging
- Regulome
- Systems Biology Markup Language (SBML)
- SBO
- Viable System Model
- Antireductionism

Systems biologists

- Category:Systems biologists

Lists

- Category:Systems biologists
- List of systems biology conferences
- List of omics topics in biology
- List of publications in systems biology
- List of systems biology research groups

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- Semantic Systems Biology (http://www.semantic-systems-biology.org)
- SystemsX.ch (http://www.systemsx.ch/) - The Swiss Initiative in Systems Biology
- Systems Biology at the Pacific Northwest National Laboratory (http://www.sysbio.org/)

Complexity

In general usage, **complexity** tends to be used to characterize something with many parts in intricate arrangement. In science there are at this time a number of approaches to characterizing complexity, many of which are reflected in this article. Seth Lloyd of M.I.T. writes that he once gave a presentation which set out 32 definitions of complexity.[1]

Definitions are often tied to the concept of a 'system' – a set of parts or elements which have relationships among them differentiated from relationships with other elements outside the relational regime. Many definitions tend to postulate or assume that complexity expresses a condition of numerous elements in a system and numerous forms of relationships among the elements. At the same time, what is complex and what is simple is relative and changes with time.

Some definitions key on the question of the probability of encountering a given condition of a system once characteristics of the system are specified. Warren Weaver has posited that the complexity of a particular system is the degree of difficulty in predicting the properties of the system if the properties of the system's parts are given. In Weaver's view, complexity comes in two forms: disorganized complexity, and organized complexity. [2] Weaver's paper has influenced contemporary thinking about complexity. [3]

The approaches which embody concepts of systems, multiple elements, multiple relational regimes, and state spaces might be summarized as implying that complexity arises from the number of distinguishable relational regimes (and their associated state spaces) in a defined system.

Some definitions relate to the algorithmic basis for the expression of a complex phenomenon or model or mathematical expression, as is later set out herein.

Disorganized complexity vs. organized complexity

One of the problems in addressing complexity issues has been distinguishing conceptually between the large number of variances in relationships extant in random collections, and the sometimes large, but smaller, number of relationships between elements in systems where constraints (related to correlation of otherwise independent elements) simultaneously reduce the

'**Map of Complexity Science**. *HERE FOR WEB VERSION OF MAP [4] **The web version of this map provides internet links to all the leading scholars and areas of research in complexity science.**
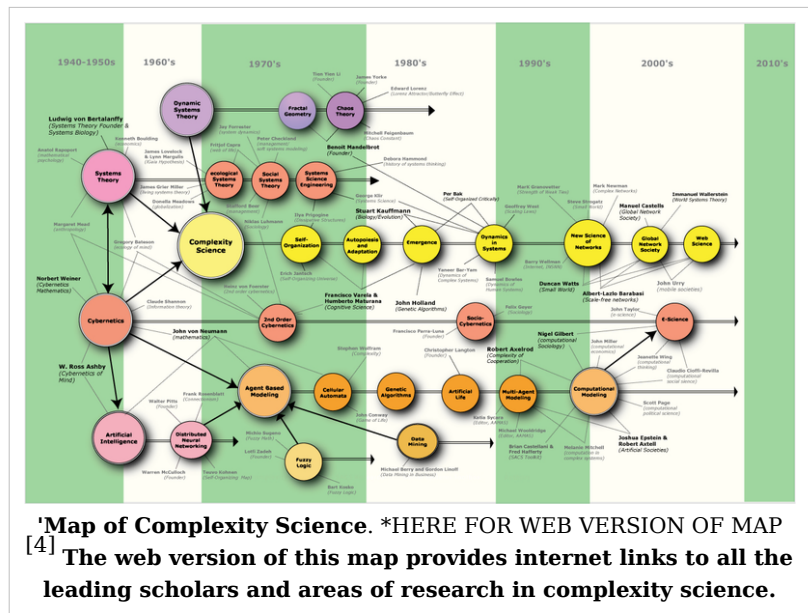
variations from element independence and create distinguishable regimes of more-uniform, or correlated, relationships, or interactions.

Weaver perceived and addressed this problem, in at least a preliminary way, in drawing a distinction between 'disorganized complexity' and 'organized complexity'.

In Weaver's view, disorganized complexity results from the particular system having a very large number of parts, say millions of parts, or many more. Though the interactions of the parts in a 'disorganized complexity' situation can be seen as largely random, the properties of the system as a whole can be understood by using probability and statistical methods.

A prime example of disorganized complexity is a gas in a container, with the gas molecules as the parts. Some would suggest that a system of disorganized complexity may be compared, for example, with the (relative) simplicity of the planetary orbits – the latter can be known by applying Newton's laws of motion, though this example involved highly correlated events.

HOW TO READ MAP:

The above map is a conceptual and historical overview of complexity science.

The Map is to be read as follows:

First, the Map is roughly historical, working as a timeline that is divided into five major periods that one can read from left to right: 1) old-school, 2) percolation, 3) the new science of complexity, 4) a work in progress, and 5) recent developments.

Each fields of study is represented as double-lined ellipse, with a double-lined arrow moving from left to the right. The relative size of these ellipses is meaningless, and is strictly a function of the space needed to write the name of each field. Double-lined arrows represent the trajectory of each field of study. Space constraints required that the length of these arrows be limited; readers should therefore assume that all of them extend outward to 2006.

The decision where to place the various fields of research respective to one another is somewhat arbitrary. However, we did try to position relative to some degree of intellectual similarity. For example, those sciences oriented toward the study of systems are located at the top of the map; the sciences that tend to extend outward from or around cyber-netics and artificial intelligence are oriented toward the development of computational method are located at the bottom.

Areas of research identified for each field of study are repre-sented as single-lined circles. As with the fields of study, the size of these circles is strictly a function of the space needed to write the different names.

The intellectual links amongst the fields of study and amongst the areas of research are represented with a bold, single-lined arrow. The head of the arrow indicates the direction of the relationship. In some cases, the relationship is mutual. To keep the map simple, rather than draw this link to the trajectory for a field of study or area of research (as in the case of the recip-rocal relationship between complexity science and agent-based modeling), we draw it to the ellipse representing the field of study or area of research.

For each area of research, we also include a short list of the leading scholars. This list is not exhaustive; but it is representa-tive, based on number of citations, general recognition, and importance in the historical development of the area of research. For each scholar we provide the following informa-tion: name, most widely known contribution, and links to key areas of research. The links amongst the scholars and their respective areas of research are represented by a dashed line. One will also note that the names of the scholars differ in font size. This was done to demonstrate their relative importance within complexity science and the sociology of complexity.

Because of the diversity of research in complexity science, we focused on the key topics in the field.

MAP LEGEND.

Organized complexity, in Weaver's view, resides in nothing else than the non-random, or correlated, interaction between the parts. These non-random, or correlated, relationships create a differentiated structure which can, as a system, interact with other systems. The coordinated system manifests properties not carried by, or dictated by, individual parts. The organized aspect of this form of complexity vis a vis other systems than the subject system can be said to "emerge," without any "guiding hand."

The number of parts does not have to be very large for a particular system to have emergent properties. A system of organized complexity may be understood in its properties (behavior among the properties) through modeling and simulation, particularly modeling and simulation with computers. An example of organized complexity is a city neighborhood as a living mechanism, with the neighborhood people among the system's parts. [5]

Sources and factors of complexity

The source of disorganized complexity is the large number of parts in the system of interest, and the lack of correlation between elements in the system.

There is no consensus at present on general rules regarding the sources of organized complexity, though the lack of randomness implies correlations between elements. See e.g. Robert Ulanowicz's treatment of ecosystems. [6] Consistent with prior statements here, the number of parts (and types of parts) in the system and the number of relations between the parts would have to be non-trivial – however, there is no general rule to separate "trivial" from "non-trivial.

Complexity of an object or system is a relative property. For instance, for many functions (problems), such a computational complexity as time of computation is smaller when multitape Turing machines are used than when Turing machines with one tape are used. Random Access Machines allow one to even more decrease time complexity (Greenlaw and Hoover 1998: 226), while inductive Turing machines can decrease even the complexity class of a function, language or set (Burgin 2005). This shows that tools of activity can be an important factor of complexity.

Specific meanings of complexity

In several scientific fields, "complexity" has a specific meaning :

- In computational complexity theory, the amounts of resources required for the execution of algorithms is studied. The most popular types of computational complexity are the time complexity of a problem equal to the number of steps that it takes to solve an instance of the problem as a function of the size of the input (usually measured in bits), using the most efficient algorithm, and the space complexity of a problem equal to the volume of the memory used by the algorithm (e.g., cells of the tape) that it takes to solve an instance of the problem as a function of the size of the input (usually measured in bits), using the most efficient algorithm. This allows to classify computational problems by complexity class (such as P, NP ...). An axiomatic approach to computational complexity was developed by Manuel Blum. It allows one to deduce many properties of concrete computational complexity measures, such as time complexity or space complexity, from properties of axiomatically defined measures.

- In algorithmic information theory, the *Kolmogorov complexity* (also called *descriptive complexity*, *algorithmic complexity* or *algorithmic entropy*) of a string is the length of the shortest binary program which outputs that string. Different kinds of Kolmogorov complexity are studied: the uniform complexity, prefix complexity, monotone complexity, time-bounded Kolmogorov complexity, and space-bounded Kolmogorov complexity. An axiomatic approach to Kolmogorov complexity based on Blum axioms (Blum 1967) was introduced by Mark Burgin in the paper presented for publication by Andrey Kolmogorov (Burgin 1982). The axiomatic approach encompasses other approaches to Kolmogorov complexity. It is possible to treat different kinds of Kolmogorov complexity as particular cases of axiomatically defined generalized Kolmogorov complexity. Instead, of proving similar theorems, such as the basic invariance theorem, for each particular measure, it is possible to easily deduce all such results from one corresponding theorem proved in the axiomatic setting. This is a general advantage of the axiomatic approach in mathematics. The axiomatic approach to Kolmogorov complexity was further developed in the book (Burgin 2005) and applied to software metrics (Burgin and Debnath, 2003; Debnath and Burgin, 2003).

- In information processing, complexity is a measure of the total number of properties transmitted by an object and detected by an observer. Such a collection of properties is often referred to as a state.

- In physical systems, complexity is a measure of the probability of the state vector of the system. This should not be confused with entropy; it is a distinct mathematical measure, one in which two distinct states are never conflated and considered equal, as is done for the notion of entropy statistical mechanics.

- In mathematics, Krohn-Rhodes complexity is an important topic in the study of finite semigroups and automata.

There are different specific forms of complexity:

- In the sense of how complicated a problem is from the perspective of the person trying to solve it, limits of complexity are measured using a term from cognitive psychology, namely the hrair limit.
- Unruly complexity denotes situations that do not have clearly defined boundaries, coherent internal dynamics, or simply mediated relations with their external context, as coined by Peter Taylor.
- Complex adaptive system denotes systems which have some or all of the following attributes [7]
  - The number of parts (and types of parts) in the system and the number of relations between the parts is non-trivial – however, there is no general rule to separate "trivial" from "non-trivial;"
  - The system has memory or includes feedback;
  - The system can adapt itself according to its history or feedback;
  - The relations between the system and its environment are non-trivial or non-linear;
  - The system can be influenced by, or can adapt itself to, its environment; and
  - The system is highly sensitive to initial conditions.

Study of complexity

Complexity has always been a part of our environment, and therefore many scientific fields have dealt with complex systems and phenomena. Indeed, some would say that only what is somehow complex – what displays variation without being random – is worthy of interest.

The use of the term complex is often confused with the term complicated. In today's systems, this is the difference between myriad connecting "stovepipes" and effective "integrated" solutions. [8] This means that complex is the opposite of independent, while complicated is the opposite of simple.

While this has led some fields to come up with specific definitions of complexity, there is a more recent movement to regroup observations from different fields to study complexity in itself, whether it appears in anthills, human brains, or stock markets. One such interndisciplinary group of fields is relational order theories.

Complexity topics

Complex behaviour

The behaviour of a complex system is often said to be due to emergence and self-organization. Chaos theory has investigated the sensitivity of systems to variations in initial conditions as one cause of complex behaviour.

Complex mechanisms

Recent developments around artificial life, evolutionary computation and genetic algorithms have led to an increasing emphasis on complexity and complex adaptive systems.

Complex simulations

In social science, the study on the emergence of macro-properties from the micro-properties, also known as macro-micro view in sociology. The topic is commonly recognized as social complexity that is often related to the use of computer simulation in social science, i.e.: computational sociology.

Complex systems

Systems theory has long been concerned with the study of complex systems (In recent times, *complexity theory* and *complex systems* have also been used as names of the field). These systems can be biological, economic, technological, etc. Recently, complexity is a natural domain of interest of the real world socio-cognitive systems and emerging systemics research. Complex systems tend to be high-dimensional, non-linear and hard to model. In specific circumstances they may exhibit low dimensional behaviour.

Complexity in data

In information theory, algorithmic information theory is concerned with the complexity of strings of data.

Complex strings are harder to compress. While intuition tells us that this may depend on the codec used to compress a string (a codec could be theoretically created in any arbitrary language, including one in which the very small command "X" could cause the computer to output a very complicated string like '18995316'"), any two Turing-complete languages can be implemented in each other, meaning that the length of two encodings in different languages will vary by at most the length of the "translation" language - which will end up being negligible for sufficiently large data strings.

These algorithmic measures of complexity tend to assign high values to random noise. However, those studying complex systems would not consider randomness as complexity.

Information entropy is also sometimes used in information theory as indicative of complexity.

Applications of complexity

Computational complexity theory is the study of the complexity of problems - that is, the difficulty of solving them. Problems can be classified by complexity class according to the time it takes for an algorithm - usually a computer program - to solve them as a function of the problem size. Some problems are difficult to solve, while others are easy. For example, some difficult problems need algorithms that take an exponential amount of time in terms of the size of the problem to solve. Take the travelling salesman problem, for example. It can be solved in time $O(n^2 2^n)$ (where *n* is the size of the network to visit - let's say the number of cities the travelling salesman must visit exactly once). As the size of the network of cities grows, the time needed to find the route grows (more than) exponentially.

Even though a problem may be computationally solvable in principle, in actual practice it may not be that simple. These problems might require large amounts of time or an inordinate amount of space. Computational complexity may be approached from many different aspects. Computational complexity can be investigated on the basis of time, memory or other resources used to solve the problem. Time and space are two of the most important and popular considerations when problems of complexity are analyzed.

There exist a certain class of problems that although they are solvable in principle they require so much time or space that it is not practical to attempt to solve them. These problems are called intractable.

There is another form of complexity called hierarchical complexity. It is orthogonal to the forms of complexity discussed so far, which are called horizontal complexity

See also

- Chaos theory
- Command and Control Research Program
- Complexity theory (disambiguation page)
- Cyclomatic complexity
- Evolution of complexity
- Game complexity
- Holism in science
- Interconnectedness
- Model of hierarchical complexity
- Occam's razor
- Process architecture
- Programming Complexity
- Sociology and complexity science
- Systems theory
- Variety (cybernetics)

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External links

- Quantifying Complexity Theory (http://www.calresco.org/lucas/quantify.htm) - classification of complex systems
- Complexity Measures (http://cscs.umich.edu/~crshalizi/notebooks/ complexity-measures.html) - an article about the abundance of not-that-useful complexity measures.
- UC Four Campus Complexity Videoconferences (http://eclectic.ss.uci.edu/~drwhite/ center/cac.html) - Human Sciences and Complexity
- Complexity Digest (http://www.comdig.com) - networking the complexity community
- The Santa Fe Institute (http://www.santafe.edu/) - engages in research in complexity related topics

Complex adaptive system

Complex adaptive systems are special cases of complex systems. They are *complex* in that they are diverse and made up of multiple interconnected elements and *adaptive* in that they have the capacity to change and learn from experience. The term *complex adaptive systems* (CAS) was coined at the interdisciplinary Santa Fe Institute (SFI), by John H. Holland, Murray Gell-Mann and others.

Overview

The term *complex adaptive systems*, or *complexity science*, is often used to describe the loosely organized academic field that has grown up around the study of such systems. Complexity science is not a single theory— it encompasses more than one theoretical framework and is highly interdisciplinary, seeking the answers to some fundamental questions about living, adaptable, changeable systems.

Examples of complex adaptive systems include the stock market, social insect and ant colonies, the biosphere and the ecosystem, the brain and the immune system, the cell and the developing embryo, manufacturing businesses and any human social group-based endeavour in a cultural and social system such as political parties or communities. There are close relationships between the field of CAS and artificial life. In both areas the principles emergence and self-organization are very important.

CAS ideas and models are essentially evolutionary, grounded in modern biological views on adaptation and evolution. The theory of complex adaptive systems bridges developments of systems theory with the ideas of generalized Darwinism, which suggests that Darwinian principles of evolution can explain a range of complex material phenomena, from cosmic to social objects.

Definitions

A CAS is a complex, self-similar collection of interacting adaptive agents. The study of CAS focuses on complex, emergent and macroscopic properties of the system. Various definitions have been offered by different researchers:

• John H. Holland

  A Complex Adaptive System (CAS) is a dynamic network of many agents (which may represent cells, species, individuals, firms, nations) acting in parallel, constantly acting and reacting to what the other agents are doing. The control of a CAS tends to be highly dispersed and decentralized. If there is to be any coherent behavior in the system, it has to arise from competition and cooperation among the agents themselves. The overall behavior of the system is the result of a huge number of decisions made every moment by many individual agents.[1]

• Kevin Dooley

  A CAS behaves/evolves according to three key principles: order is emergent as opposed to predetermined (c.f. Neural Networks), the system's history is irreversible, and the system's future is often unpredictable. The basic building blocks of the CAS are agents. Agents scan their environment and develop schema representing interpretive and action rules. These schema are subject to change and evolution.[2]

- Other definitions

    Macroscopic collections of simple (and typically nonlinearly) interacting units that are endowed with the ability to evolve and adapt to a changing environment.[3]

General properties

What distinguishes a CAS from a pure multi-agent system (MAS) is the focus on top-level properties and features like self-similarity, complexity, emergence and self-organization. A MAS is simply defined as a system composed of multiple, interacting agents. In CASs, the agents as well as the system are adaptive: the system is self-similar. A CAS is a complex, self-similar collectivity of interacting adaptive agents. Complex Adaptive Systems are

Complex Adaptive System

characterised by a high degree of adaptive capacity, giving them resilience in the face of perturbation.

Other important properties are adaptation (or homeostasis), communication, cooperation, specialization, spatial and temporal organization, and of course reproduction. They can be found on all levels: cells specialize, adapt and reproduce themselves just like larger organisms do. Communication and cooperation take place on all levels, from the agent to the system level. The forces driving co-operation between agents in such a system can be analysed with game theory. many of the issues of compelixty science and new tools for the anlysis of complexity are being developed within Network Science.
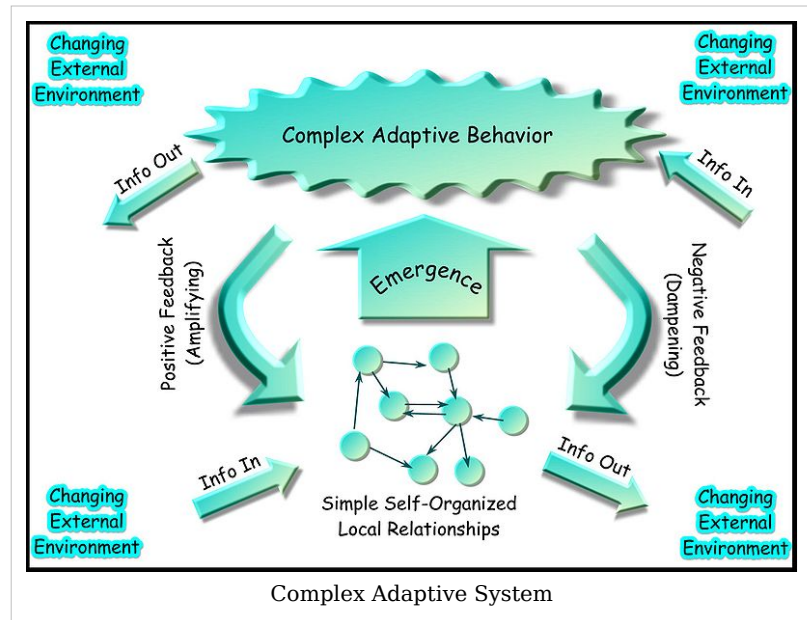
Evolution of complexity

Living organisms are complex adaptive systems. Although complexity is hard to quantify in biology, evolution has produced some remarkably complex organisms.[4] This observation has led to the common idea of evolution being progressive and leading towards what are viewed as "higher organisms".[5]

If this were generally true, evolution would possess an active trend towards complexity. As shown below, in this type of process the value of the most common amount of complexity would increase over time.[6] Indeed, some artificial life simulations have suggested that the generation of CAS is an inescapable feature of evolution.[7] [8]

Passive versus active trends in the evolution of complexity. CAS at the beginning of the processes are colored red. Changes in the number of systems are shown by the height of the bars, with each set of graphs moving up in a time series.
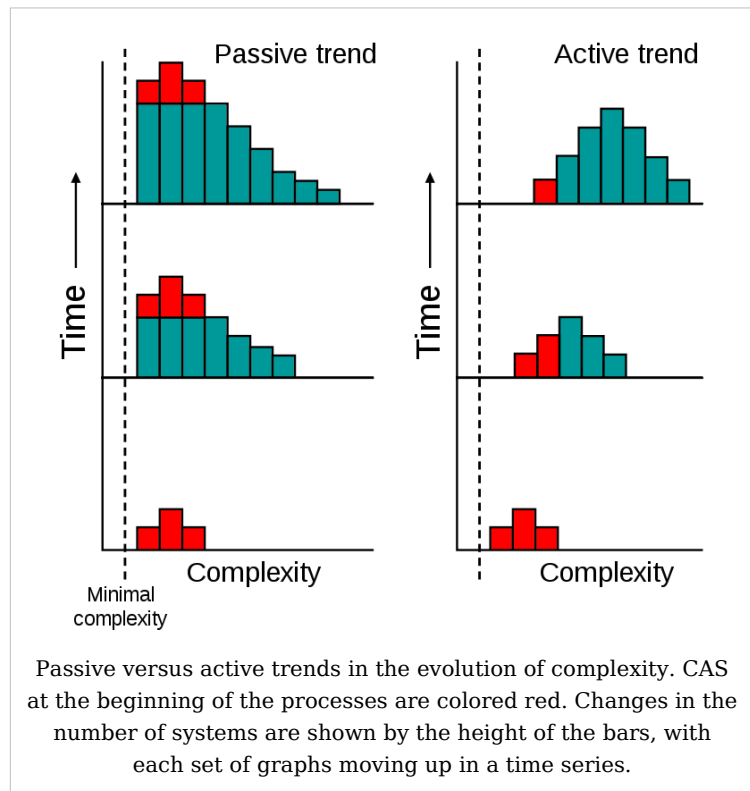
However, the idea of a general trend towards complexity in evolution can also be explained through a passive process.[6] This involves an increase in variance but the most common value, the mode, does not change. Thus, the maximum level of complexity increases over time, but only as an indirect product of there being more organisms in total. This type of random process is also called a bounded random walk.

In this hypothesis, the apparent trend towards more complex organisms is an illusion resulting from concentrating on the small number of large, very complex organisms that inhabit the right-hand tail of the complexity distribution and ignoring simpler and much more common organisms. This passive model emphasizes that the overwhelming majority of species are microscopic prokaryotes,[9] which comprise about half the world's biomass,[10] constitute the vast majority of Earth's biodiversity.[11] Therefore, simple life remains dominant on Earth, and complex life appears more diverse only because of sampling bias.

This lack of an overall trend towards complexity in biology does not preclude the existence of forces driving systems towards complexity in a subset of cases. These minor trends are balanced by other evolutionary pressures that drive systems towards less complex states.

See also

- Artificial life

- Center for Complex Systems and Brain Sciences

- Center for Social Dynamics & Complexity (CSDC) at Arizona State University [12]

- Enterprise systems engineering

- Generative sciences

- Santa Fe Institute

- Cognitive Science
- Command and Control Research Program
- Computational Sociology

- Simulated reality
- Sociology and complexity science
- Swarm Development Group

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- DNA Wales Research Group (http://www.dnawales.co.uk/) Current Research in Organisational change CAS/CES related news and free research data. Also linked to the Business Doctor & BBC documentary series
- A description (http://pespmc1.vub.ac.be/CAS.html) of complex adaptive systems on the Principia Cybernetica Web.
- Quick reference (http://bactra.org/notebooks/complexity.html) single-page description of the 'world' of complexity and related ideas hosted by the Center for the Study of Complex Systems at the University of Michigan.
- Complex systems research network (http://www.complexsystems.net.au/)
- The Open Agent-Based Modeling Consortium (http://www.openabm.org/site/)

Biostatistics

Biostatistics (a combination of the words biology and statistics; sometimes referred to as **biometry** or **biometrics**) is the application of statistics to a wide range of topics in biology. The science of biostatistics encompasses the design of biological experiments, especially in medicine and agriculture; the collection, summarization, and analysis of data from those experiments; and the interpretation of, and inference from, the results.

Biostatistics and the history of biological thought

Biostatistical reasoning and modeling were of critical importance to the foundation theories of modern biology. In the early 1900s, after the rediscovery of Mendel's work, the conceptual gaps in understanding between genetics and evolutionary Darwinism led to vigorous debate between biometricians such as Walter Weldon and Karl Pearson and Mendelians such as Charles Davenport, William Bateson and Wilhelm Johannsen. By the 1930s statisticians and models built on statistical reasoning had helped to resolve these differences and to produce the neo-Darwinian modern evolutionary synthesis.

The leading figures in the establishment of this synthesis all relied on statistics and developed its use in biology.

- Sir Ronald A. Fisher developed several basic statistical methods in support of his work *The Genetical Theory of Natural Selection*
- Sewall G. Wright used statistics in the development of modern population genetics
- J. B. S Haldane's book, *The Causes of Evolution*, reestablished natural selection as the premier mechanism of evolution by explaining it in terms of the mathematical consequences of Mendelian genetics.

These individuals and the work of other biostatisticians, mathematical biologists, and statistically inclined geneticists helped bring together evolutionary biology and genetics into a consistent, coherent whole that could begin to be quantitatively modeled.

In parallel to this overall development, the pioneering work of D'Arcy Thompson in *On Growth and Form* also helped to add quantitative discipline to biological study.

Despite the fundamental importance and frequent necessity of statistical reasoning, there may nonetheless have been a tendency among biologists to distrust or deprecate results which are not qualitatively apparent. One anecdote describes Thomas Hunt Morgan banning the Frieden calculator from his department at Caltech, saying "Well, I am like a guy who is prospecting for gold along the banks of the Sacramento River in 1849. With a little intelligence, I can reach down and pick up big nuggets of gold. And as long as I can do that, I'm not going to let any people in my department waste scarce resources in placer mining."[1] Educators are now adjusting their curricula to focus on more quantitative concepts and tools.[2]

Education and training programs

Almost all educational programmes in biostatistics are at postgraduate level. They are most often found in schools of public health, affiliated with schools of medicine, forestry, or agriculture or as a focus of application in departments of statistics.

In the United States, while several universities have dedicated biostatistics departments, many other top-tier universities integrate biostatistics faculty into statistics or other departments, such as epidemiology. Thus departments carrying the name "biostatistics" may exist under quite different structures. For instance, relatively new biostatistics departments have been founded with a focus on bioinformatics and computational biology, whereas older departments, typically affiliated with schools of public health, will have more traditional lines of research involving epidemiological studies and clinical trials as well as bioinformatics. In larger universities where both a statistics and a biostatistics department exist, the degree of integration between the two departments may range from the bare minimum to very close collaboration. In general, the difference between a statistics program and a biostatistics one is twofold: (i) statistics departments will often host theoretical/methodological research which are less common in biostatistics programs and (ii) statistics departments have lines of research that may include biomedical applications but also other areas such as industry (quality control), business and economics and biological areas other than medicine.

Applications of biostatistics

- Public health, including epidemiology, health services research, nutrition, and environmental health
- Design and analysis of clinical trials in medicine
- Genomics, population genetics, and statistical genetics in populations in order to link variation in genotype with a variation in phenotype. This has been used in agriculture to improve crops and farm animals (animal breeding). In biomedical research, this work can assist in finding candidates for gene alleles that can cause or influence predisposition to disease in human genetics
- Ecology, ecological forecasting
- Biological sequence analysis

Statistical methods are beginning to be integrated into medical informatics, public health informatics, and bioinformatics

Biostatistics journals

- *Biometrics*
- *Biometrika*
- *Biostatistics*
- *International Journal of Biostatistics, The*
- *Journal of Agricultural, Biological, and Environmental Statistics*
- *Journal of Biopharmaceutical Statistics*
- *Pharmaceutical Statistics*
- *Statistical Applications in Genetics and Molecular Biology*
- *Statistics in Biopharmaceutical Research*
- *Statistics in Medicine*

- *Turkiye Klinikleri Journal of Biostatistics*

Related fields

Biostatistics shares several methods with quantitative fields such as:

- statistics,
- operations research,
- computer science,
- psychometrics,
- econometrics, and
- mathematical demography

See also

- Quantitative parasitology
- Ecological forecasting

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[2] http://www.reinventioncenter.miami.edu/Spotlights/BioMath.htm|"Spotlight:application of quantitative
    concepts and techniques in undergraduate biology". http://www.reinventioncenter.miami.edu/Spotlights/
    BioMath.htm.

External links

- The International Biometric Society (http://www.tibs.org)
- The Collection of Biostatistics Research Archive (http://www.biostatsresearch.com/
  repository/)
- Guide to Biostatistics (MedPageToday.com) (http://www.medpagetoday.com/
  Medpage-Guide-to-Biostatistics.pdf)
- Biostatistician (http://biostatistician.eu)

Journals

- Statistical Applications in Genetics and Molecular Biology (http://www.bepress.com/
  sagmb/)
- Statistics in Medicine (http://www3.interscience.wiley.com/cgi-bin/jhome/2988)
- The International Journal of Biostatistics (http://www.bepress.com/ijb/)
- Journal of Agricultural, Biological, and Environmental Statistics (http://www.amstat.
  org/publications/jabes/)
- Journal of Biopharmaceutical Statistics (http://www.tandf.co.uk/journals/titles/
  10543406.asp)
- Biostatistics (http://www.biostatistics.oxfordjournals.org/)
- Biometrics (http://www.tibs.org/biometrics/)
- Biometrika (http://biomet.oxfordjournals.org/)
- Biometrical Journal (http://www.biometrical-journal.de/)
- Genetics Selection Evolution (http://www.gse-journal.org/)

Bioinformatics

Bioinformatics is the application of information technology to the field of molecular biology. The term *bioinformatics* was coined by Paulien Hogeweg in 1978 for the study of informatic processes in biotic systems. Bioinformatics now entails the creation and advancement of databases, algorithms, computational and statistical techniques, and theory to solve formal and practical problems arising from the management and analysis of biological data. Over the past few decades rapid developments in genomic and other molecular research technologies and developments in information technologies have combined to produce a tremendous amount of information related to molecular biology. It is the name given to these mathematical and computing approaches used to glean understanding of biological processes. Common activities in bioinformatics include mapping and analyzing DNA and protein sequences, aligning different DNA and protein sequences to compare them and creating and viewing 3-D models of protein structures.

Map of the human X chromosome (from the NCBI website). Assembly of the human genome is one of the greatest achievements of bioinformatics.

The primary goal of bioinformatics is to increase our understanding of biological processes. What sets it apart from other approaches, however, is its focus on developing and applying computationally intensive techniques (e.g., data mining, machine learning algorithms, and visualization) to achieve this goal. Major research efforts in the field include sequence alignment, gene finding, genome assembly, protein structure alignment, protein structure prediction, prediction of gene expression and protein-protein interactions, genome-wide association studies and the modeling of evolution.

Introduction

Bioinformatics was applied in the creation and maintenance of a database to store biological information at the beginning of the "genomic revolution", such as nucleotide and amino acid sequences. Development of this type of database involved not only design issues but the development of complex interfaces whereby researchers could both access existing data as well as submit new or revised data.

In order to study how normal cellular activities are altered in different disease states, the biological data must be combined to form a comprehensive picture of these activities. Therefore, the field of bioinformatics has evolved such that the most pressing task now involves the analysis and interpretation of various types of data, including nucleotide and amino acid sequences, protein domains, and protein structures. The actual process of analyzing and interpreting data is referred to as computational biology. Important sub-disciplines within bioinformatics and computational biology include:
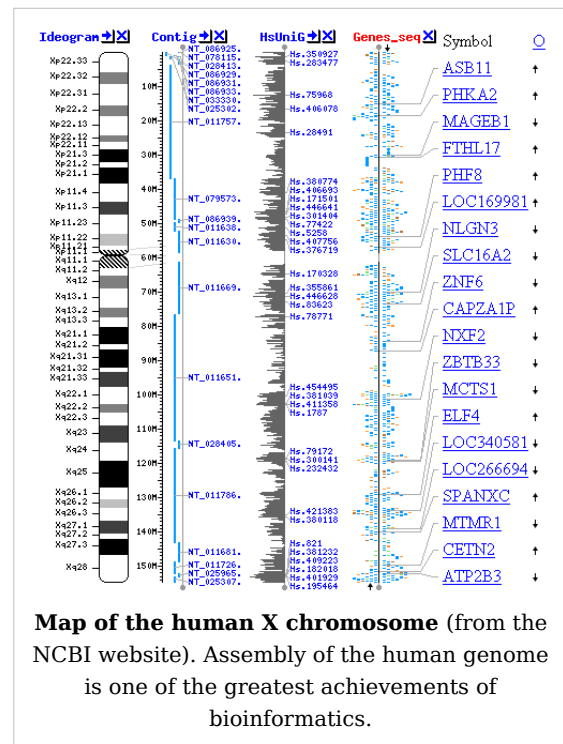
a) the development and implementation of tools that enable efficient access to, and use and management of, various types of information. **b)** the development of new algorithms (mathematical formulas) and statistics with which to assess relationships among members of large data sets, such as methods to locate a gene within a sequence, predict protein structure and/or function, and cluster protein sequences into families of related sequences.

Major research areas

Sequence analysis

Since the Phage Φ-X174 was sequenced in 1977, the DNA sequences of hundreds of organisms have been decoded and stored in databases. The information is analyzed to determine genes that encode polypeptides, as well as regulatory sequences. A comparison of genes within a species or between different species can show similarities between protein functions, or relations between species (the use of molecular systematics to construct phylogenetic trees). With the growing amount of data, it long ago became impractical to analyze DNA sequences manually. Today, computer programs are used to search the genome of thousands of organisms, containing billions of nucleotides. These programs would compensate for mutations (exchanged, deleted or inserted bases) in the DNA sequence, in order to identify sequences that are related, but not identical. A variant of this sequence alignment is used in the sequencing process itself. The so-called shotgun sequencing technique (which was used, for example, by The Institute for Genomic Research to sequence the first bacterial genome, *Haemophilus influenzae*) does not give a sequential list of nucleotides, but instead the sequences of thousands of small DNA fragments (each about 600-800 nucleotides long). The ends of these fragments overlap and, when aligned in the right way, make up the complete genome. Shotgun sequencing yields sequence data quickly, but the task of assembling the fragments can be quite complicated for larger genomes. In the case of the Human Genome Project, it took several days of CPU time (on one hundred Pentium III desktop machines clustered specifically for the purpose) to assemble the fragments. Shotgun sequencing is the method of choice for virtually all genomes sequenced today, and genome assembly algorithms are a critical area of bioinformatics research.

Another aspect of bioinformatics in sequence analysis is the automatic search for genes and regulatory sequences within a genome. Not all of the nucleotides within a genome are genes. Within the genome of higher organisms, large parts of the DNA do not serve any obvious purpose. This so-called junk DNA may, however, contain unrecognized functional elements. Bioinformatics helps to bridge the gap between genome and proteome projects--for example, in the use of DNA sequences for protein identification.

See also: sequence analysis, sequence profiling tool, sequence motif.

Genome annotation

In the context of genomics, **annotation** is the process of marking the genes and other biological features in a DNA sequence. The first genome annotation software system was designed in 1995 by Dr. Owen White, who was part of the team that sequenced and analyzed the first genome of a free-living organism to be decoded, the bacterium *Haemophilus influenzae*. Dr. White built a software system to find the genes (places in the DNA sequence that encode a protein), the transfer RNA, and other features, and to make

initial assignments of function to those genes. Most current genome annotation systems work similarly, but the programs available for analysis of genomic DNA are constantly changing and improving.

Computational evolutionary biology

Evolutionary biology is the study of the origin and descent of species, as well as their change over time. Informatics has assisted evolutionary biologists in several key ways; it has enabled researchers to:

- trace the evolution of a large number of organisms by measuring changes in their DNA, rather than through physical taxonomy or physiological observations alone,
- more recently, compare entire genomes, which permits the study of more complex evolutionary events, such as gene duplication, horizontal gene transfer, and the prediction of factors important in bacterial speciation,
- build complex computational models of populations to predict the outcome of the system over time
- track and share information on an increasingly large number of species and organisms

Future work endeavours to reconstruct the now more complex tree of life.

The area of research within computer science that uses genetic algorithms is sometimes confused with computational evolutionary biology, but the two areas are unrelated.

Measuring biodiversity

Biodiversity of an ecosystem might be defined as the total genomic complement of a particular environment, from all of the species present, whether it is a biofilm in an abandoned mine, a drop of sea water, a scoop of soil, or the entire biosphere of the planet Earth. Databases are used to collect the species names, descriptions, distributions, genetic information, status and size of populations, habitat needs, and how each organism interacts with other species. Specialized software programs are used to find, visualize, and analyze the information, and most importantly, communicate it to other people. Computer simulations model such things as population dynamics, or calculate the cumulative genetic health of a breeding pool (in agriculture) or endangered population (in conservation). One very exciting potential of this field is that entire DNA sequences, or genomes of endangered species can be preserved, allowing the results of Nature's genetic experiment to be remembered *in silico*, and possibly reused in the future, even if that species is eventually lost.[1]

Analysis of gene expression

The expression of many genes can be determined by measuring mRNA levels with multiple techniques including microarrays, expressed cDNA sequence tag (EST) sequencing, serial analysis of gene expression (SAGE) tag sequencing, massively parallel signature sequencing (MPSS), or various applications of multiplexed in-situ hybridization. All of these techniques are extremely noise-prone and/or subject to bias in the biological measurement, and a major research area in computational biology involves developing statistical tools to separate signal from noise in high-throughput gene expression studies. Such studies are often used to determine the genes implicated in a disorder: one might compare microarray data from cancerous epithelial cells to data from non-cancerous cells to determine the transcripts that are up-regulated and down-regulated in a particular population of cancer

cells.

Analysis of regulation

Regulation is the complex orchestration of events starting with an extracellular signal such as a hormone and leading to an increase or decrease in the activity of one or more proteins. Bioinformatics techniques have been applied to explore various steps in this process. For example, promoter analysis involves the identification and study of sequence motifs in the DNA surrounding the coding region of a gene. These motifs influence the extent to which that region is transcribed into mRNA. Expression data can be used to infer gene regulation: one might compare microarray data from a wide variety of states of an organism to form hypotheses about the genes involved in each state. In a single-cell organism, one might compare stages of the cell cycle, along with various stress conditions (heat shock, starvation, etc.). One can then apply clustering algorithms to that expression data to determine which genes are co-expressed. For example, the upstream regions (promoters) of co-expressed genes can be searched for over-represented regulatory elements.

Analysis of protein expression

Protein microarrays and high throughput (HT) mass spectrometry (MS) can provide a snapshot of the proteins present in a biological sample. Bioinformatics is very much involved in making sense of protein microarray and HT MS data; the former approach faces similar problems as with microarrays targeted at mRNA, the latter involves the problem of matching large amounts of mass data against predicted masses from protein sequence databases, and the complicated statistical analysis of samples where multiple, but incomplete peptides from each protein are detected.

Analysis of mutations in cancer

In cancer, the genomes of affected cells are rearranged in complex or even unpredictable ways. Massive sequencing efforts are used to identify previously unknown point mutations in a variety of genes in cancer. Bioinformaticians continue to produce specialized automated systems to manage the sheer volume of sequence data produced, and they create new algorithms and software to compare the sequencing results to the growing collection of human genome sequences and germline polymorphisms. New physical detection technology are employed, such as oligonucleotide microarrays to identify chromosomal gains and losses (called comparative genomic hybridization), and single nucleotide polymorphism arrays to detect known *point mutations*. These detection methods simultaneously measure several hundred thousand sites throughout the genome, and when used in high-throughput to measure thousands of samples, generate terabytes of data per experiment. Again the massive amounts and new types of data generate new opportunities for bioinformaticians. The data is often found to contain considerable variability, or noise, and thus Hidden Markov model and change-point analysis methods are being developed to infer real copy number changes.

Another type of data that requires novel informatics development is the analysis of lesions found to be recurrent among many tumors .

Prediction of protein structure

Protein structure prediction is another important application of bioinformatics. The amino acid sequence of a protein, the so-called primary structure, can be easily determined from the sequence on the gene that codes for it. In the vast majority of cases, this primary structure uniquely determines a structure in its native environment. (Of course, there are exceptions, such as the bovine spongiform encephalopathy - aka Mad Cow Disease - prion.) Knowledge of this structure is vital in understanding the function of the protein. For lack of better terms, structural information is usually classified as one of *secondary*, *tertiary* and *quaternary* structure. A viable general solution to such predictions remains an open problem. As of now, most efforts have been directed towards heuristics that work most of the time.

One of the key ideas in bioinformatics is the notion of homology. In the genomic branch of bioinformatics, homology is used to predict the function of a gene: if the sequence of gene *A*, whose function is known, is homologous to the sequence of gene *B,* whose function is unknown, one could infer that B may share A's function. In the structural branch of bioinformatics, homology is used to determine which parts of a protein are important in structure formation and interaction with other proteins. In a technique called homology modeling, this information is used to predict the structure of a protein once the structure of a homologous protein is known. This currently remains the only way to predict protein structures reliably.

One example of this is the similar protein homology between hemoglobin in humans and the hemoglobin in legumes (leghemoglobin). Both serve the same purpose of transporting oxygen in the organism. Though both of these proteins have completely different amino acid sequences, their protein structures are virtually identical, which reflects their near identical purposes.

Other techniques for predicting protein structure include protein threading and *de novo* (from scratch) physics-based modeling.

See also: structural motif and structural domain.

Comparative genomics

The core of comparative genome analysis is the establishment of the correspondence between genes (orthology analysis) or other genomic features in different organisms. It is these intergenomic maps that make it possible to trace the evolutionary processes responsible for the divergence of two genomes. A multitude of evolutionary events acting at various organizational levels shape genome evolution. At the lowest level, point mutations affect individual nucleotides. At a higher level, large chromosomal segments undergo duplication, lateral transfer, inversion, transposition, deletion and insertion. Ultimately, whole genomes are involved in processes of hybridization, polyploidization and endosymbiosis, often leading to rapid speciation. The complexity of genome evolution poses many exciting challenges to developers of mathematical models and algorithms, who have recourse to a spectra of algorithmic, statistical and mathematical techniques, ranging from exact, heuristics, fixed parameter and approximation algorithms for problems based on parsimony models to Markov Chain Monte Carlo algorithms for Bayesian analysis of problems based on probabilistic models.

Many of these studies are based on the homology detection and protein families computation.

Modeling biological systems

Systems biology involves the use of computer simulations of cellular subsystems (such as the networks of metabolites and enzymes which comprise metabolism, signal transduction pathways and gene regulatory networks) to both analyze and visualize the complex connections of these cellular processes. Artificial life or virtual evolution attempts to understand evolutionary processes via the computer simulation of simple (artificial) life forms.

High-throughput image analysis

Computational technologies are used to accelerate or fully automate the processing, quantification and analysis of large amounts of high-information-content biomedical imagery. Modern image analysis systems augment an observer's ability to make measurements from a large or complex set of images, by improving accuracy, objectivity, or speed. A fully developed analysis system may completely replace the observer. Although these systems are not unique to biomedical imagery, biomedical imaging is becoming more important for both diagnostics and research. Some examples are:

- high-throughput and high-fidelity quantification and sub-cellular localization (high-content screening, cytohistopathology)
- morphometrics
- clinical image analysis and visualization
- determining the real-time air-flow patterns in breathing lungs of living animals
- quantifying occlusion size in real-time imagery from the development of and recovery during arterial injury
- making behavioral observations from extended video recordings of laboratory animals
- infrared measurements for metabolic activity determination
- inferring clone overlaps in DNA mapping, e.g. the Sulston score

Protein-protein docking

In the last two decades, tens of thousands of protein three-dimensional structures have been determined by X-ray crystallography and Protein nuclear magnetic resonance spectroscopy (protein NMR). One central question for the biological scientist is whether it is practical to predict possible protein-protein interactions only based on these 3D shapes, without doing protein-protein interaction experiments. A variety of methods have been developed to tackle the Protein-protein docking problem, though it seems that there is still much work to be done in this field.

Software and tools

Software tools for bioinformatics range from simple command-line tools, to more complex graphical programs and standalone web-services available from various bioinformatics companies or public institutions. The computational biology tool best-known among biologists is probably BLAST, an algorithm for determining the similarity of arbitrary sequences against other sequences, possibly from curated databases of protein or DNA sequences. BLAST is one of a number of generally available programs for doing sequence alignment. The NCBI provides a popular web-based implementation that searches their databases.

Web services in bioinformatics

SOAP and REST-based interfaces have been developed for a wide variety of bioinformatics applications allowing an application running on one computer in one part of the world to use algorithms, data and computing resources on servers in other parts of the world. The main advantages lay in the end user not having to deal with software and database maintenance overheads. Basic bioinformatics services are classified by the EBI into three categories: SSS (Sequence Search Services), MSA (Multiple Sequence Alignment) and BSA (Biological Sequence Analysis). The availability of these service-oriented bioinformatics resources demonstrate the applicability of web based bioinformatics solutions, and range from a collection of standalone tools with a common data format under a single, standalone or web-based interface, to integrative, distributed and extensible bioinformatics workflow management systems.

See also

Related topics

- Biocybernetics
- Bioinformatics companies
- Biologically inspired computing
- Biomedical informatics
- Computational biology
- Computational biomodeling
- Computational genomics
- DNA sequencing theory
- Dot plot (bioinformatics)
- Dry lab
- Margaret Oakley Dayhoff
- Metabolic network modelling
- Molecular Design software
- Morphometrics
- Natural computation
- Pharmaceutical company
- Protein-protein interaction prediction
- List of nucleic acid simulation software
- List of numerical analysis software
- List of protein structure prediction software
- List of scientific journals in bioinformatics

Related fields

- Applied mathematics
- Artificial intelligence
- Biology
- Cheminformatics
- Clinomics
- Comparative genomics
- Computational biology
- Computational epigenetics
- Computational science
- Computer science
- Cybernetics
- Ecoinformatics
- Genomics
- Informatics
- Information theory
- Mathematical biology
- Molecular modelling
- Neuroinformatics
- Proteomics
- Pervasive adaptation
- Scientific computing
- Statistics
- Structural biology
- Systems biology
- Theoretical biology
- Veterinary informatics

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- Computational Biology: Genomes, Networks, Evolution Free MIT Course (http://ocw.mit.edu/OcwWeb/Electrical-Engineering-and-Computer-Science/6-895Fall-2005/CourseHome/index.htm)
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External links

- Major Organizations
  - Bioinformatics Organization (Bioinformatics.Org): The Open-Access Institute (http://bioinformatics.org/)
  - EMBnet (http://www.embnet.org/)
  - European Bioinformatics Institute (http://www.ebi.ac.uk/)
  - European Molecular Biology Laboratory (http://www.embl.org/)
  - The International Society for Computational Biology (http://www.iscb.org/)
  - National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/)
  - National Institutes of Health homepage (http://www.nih.gov)
  - Open Bioinformatics Foundation: umbrella non-profit organization supporting certain open-source projects in bioinformatics (http://www.open-bio.org/)
  - Swiss Institute of Bioinformatics
  - Wellcome Trust Sanger Institute
- Major Journals
  - Algorithms in Molecular Biology (http://www.almob.org/)
  - Bioinformatics (http://bioinformatics.oupjournals.org/)
  - BMC Bioinformatics (http://www.biomedcentral.com/bmcbioinformatics)
  - Briefings in Bioinformatics (http://bib.oxfordjournals.org/)
  - Journal of Advanced Research in Bioinformatics (http://www.i-asr.org/jarb.html)
  - Evolutionary Bioinformatics (http://www.la-press.com/evolbio.htm)
  - Genome Research (http://www.genome.org)
  - The International Journal of Biostatistics (http://www.bepress.com/ijb/)
  - Journal of Computational Biology (http://www.liebertpub.com/publication.aspx?pub_id=31)
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  - Molecular Systems Biology (http://www.nature.com/msb/index.html)
  - PLoS Computational Biology (http://compbiol.plosjournals.org)
  - Statistical Applications in Genetic and Molecular Biology (http://www.bepress.com/sagmb/)
  - Transactions on Computational Biology and Bioinformatics - IEEE/ACM (http://www.computer.org/tcbb/)
  - International Journal of Bioinformatics Research and Applications (http://www.inderscience.com/browse/index.php?journalcode=ijbra)
  - List of Bioinformatics journals (http://www.bioinformatics.fr/journals.php) at Bioinformatics.fr
  - EMBnet.News (http://www.embnet.org) at EMBnet.org
  - International Journal of Computational Biology and Drug Design (IJCBDD)
  - International Journal of Functional Informatics and Personalized Medicine (IJFIPM)
- Other sites
  - The exhaustive bioinformatics information resource directory including servers, tools, database links and bioinformatics companies (http://bionet.awardspace.info/)

- The Collection of Biostatistics Research Archive (http://www.biostatsresearch.com/repository/)
- Human Genome Project and Bioinformatics (http://www.ornl.gov/TechResources/Human_Genome/research/informatics.html)
- List of Bioinformatics Research Groups (http://www.bioinformatics.fr/laboratories.php) at Bioinformatics.fr
- List of Bioinformatics Research Groups (http://www.dmoz.org/Science/Biology/Bioinformatics/Research_Groups//) at the Open Directory Project
- Tutorials / Resources / Primers
  - Bioinformatics - A Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/bioinformatics.html) — by NCBI
  - A bioinformatics directory (http://bioinformatics.co.nr/)

See also

- International Society of Intelligent Biological Medicine (ISIBM)

Biocybernetics

Biocybernetics is the application of cybernetics to biological science, composed of biological disciplines that benefit from the application of cybernetics: neurology, multicellular systems and others. Biocybernetics plays a major role in systems biology, seeking to integrate different levels of information to understand how biological systems function.

Biocybernetics as an abstract science is a part of theoretical biology, and based upon the principles of systemics.

Terminology

Biocybernetics is a cojoined word from bio (Greek: βίο / life) and cybernetics (Greek: κυβερνητική / controlling-governing). It is sometimes written together or with a blank or written fully as biological cybernetics, whilst the same rules apply. Most write it together though, as Google statistics show. The same applies to neuro cybernetics which should also be looked up as neurological, when doing extensive research.

Same or familiar fields

As those disciplines are dealing on theoretical/abstract foundations and are in accordance with the popularity of computers. Thus papers and research is in greater numbers going on under different names: e.g. molecular cybernetics -> molecular computational systems OR molecular systems theory OR molecular systemics OR molecular information/informational systems

Please heed this when you engage in an extensive search for information to assure access to a broad range of papers.

Categories

- biocybernetics - the study of an entire living organism
- neurocybernetics - cybernetics dealing with neurological models. (psycho-cybernetics was the title of a self-help book, and is not a scientific discipline)
- molecular cybernetics - cybernetics dealing with molecular systems (e.g. molecular biology cybernetics)
- cellular cybernetics - cybernetics dealing with cellular systems (e.g. information technology/cell phones,.. or biological cells)
- evolutionary cybernetics - study of the evolution of informational systems (See also evolutionary programming, evolutionary algorithm)
- any distinct informational system within the realm of biology

See also

- Bioinformatics
- Biosemiotics
- Computational biology
- Computational biomodeling
- Medical cybernetics

References

External links

- Journal "Biological Cybernetics" [1]
- Scientific portal on biological cybernetics [2]
- UCLA Biocybernetics Laboratory [3]

References

[1] http://www.springerlink.com/link.asp?id=100465
[2] http://www.biological-cybernetics.de
[3] http://biocyb.cs.ucla.edu/research.html

Molecular dynamics

Molecular dynamics (**MD**) is a form of computer simulation in which atoms and molecules are allowed to interact for a period of time by approximations of known physics, giving a view of the motion of the atoms. Because molecular systems generally consist of a vast number of particles, it is impossible to find the properties of such complex systems analytically. When the number of bodies are more than two no analytical solutions can be found and result in chaotic motion (see n-body problem). MD simulation circumvents this problem by using numerical methods. It represents an interface between laboratory experiments and theory, and can be understood as a "virtual experiment". MD probes the relationship between molecular structure, movement and function. Molecular dynamics is a multidisciplinary method. Its laws and theories stem from mathematics, physics, and chemistry, and it employs algorithms from computer science and information theory. It was originally conceived within theoretical physics in the late 1950s[1] and early 1960s [2] , but is applied today mostly in materials science and modeling of biomolecules.

Before it became possible to simulate molecular dynamics with computers, some undertook the hard work of trying it with physical models such as macroscopic spheres. The idea was to arrange them to replicate the properties of a liquid. J.D. Bernal said, in 1962: "... I took a number of rubber balls and stuck them together with rods of a selection of different lengths ranging from 2.75 to 4 inches. I tried to do this in the first place as casually as possible, working in my own office, being interrupted every five minutes or so and not remembering what I had done before the interruption."[3] Fortunately, now computers keep track of bonds during a simulation.

Molecular dynamics is a specialized discipline of molecular modeling and computer simulation based on statistical mechanics; the main justification of the MD method is that statistical ensemble averages are equal to time averages of the system, known as the ergodic hypothesis. MD has also been termed "statistical mechanics by numbers" and "Laplace's vision of Newtonian mechanics" of predicting the future by animating nature's forces[4] [5] and allowing insight into molecular motion on an atomic scale. However, long MD simulations are mathematically ill-conditioned, generating cumulative errors in numerical integration that can be minimized with proper selection of algorithms and parameters, but not eliminated entirely. Furthermore, current potential functions are, in many cases, not sufficiently accurate to reproduce the dynamics of molecular systems, so the much more computationally demanding Ab Initio Molecular Dynamics method must be used. Nevertheless, molecular dynamics techniques allow detailed time and space resolution into representative behavior in phase space.

Areas of Application

There is a significant difference between the focus and methods used by chemists and physicists, and this is reflected in differences in the jargon used by the different fields. In chemistry and biophysics, the interaction between the particles is either described by a "force field" (**classical MD**), a quantum chemical model, or a mix between the two. These terms are not used in physics, where the interactions are usually described by the name of the theory or approximation being used and called the potential energy, or just "potential".

Give atoms initial positions $r^{(t=0)}$, choose short Δt
Get forces $\boldsymbol{F} = -\nabla\ V(\boldsymbol{r}^{(i)})$ and $\boldsymbol{a} = \boldsymbol{F}/m$
Move atoms: $\boldsymbol{r}^{(i+1)} = \boldsymbol{r}^{(i)} + \boldsymbol{v}^{(i)}\,\Delta t + \tfrac{1}{2}\,\boldsymbol{a}\,\Delta t^2 + \ldots$
Move time forward: $t = t + \Delta t$
Repeat as long as you need

Highly simplified description of the molecular dynamics simulation algorithm. The simulation proceeds iteratively by alternatively calculating forces and solving the equations of motion based on the accelerations obtained from the new forces. In practise, almost all MD codes use much more complicated versions of the algorithm, including two steps (predictor and corrector) in solving the equations of motion and many additional steps for e.g. temperature and pressure control, analysis and output.

Beginning in theoretical physics, the method of MD gained popularity in materials science and since the 1970s also in biochemistry and biophysics. In chemistry, MD serves as an important tool in protein structure determination and refinement using experimental tools such as X-ray crystallography and NMR. It has also been applied with limited success as a method of refining protein structure predictions. In physics, MD is used to examine the dynamics of atomic-level phenomena that cannot be observed directly, such as thin film growth and ion-subplantation. It is also used to examine the physical properties of nanotechnological devices that have not or cannot yet be created.

In applied mathematics and theoretical physics, molecular dynamics is a part of the research realm of dynamical systems, ergodic theory and statistical mechanics in general. The concepts of energy conservation and molecular entropy come from thermodynamics. Some techniques to calculate conformational entropy such as principal components analysis come from information theory. Mathematical techniques such as the transfer operator become applicable when MD is seen as a Markov chain. Also, there is a large community of mathematicians working on volume preserving, symplectic integrators for more computationally efficient MD simulations.

MD can also be seen as a special case of the discrete element method (DEM) in which the particles have spherical shape (e.g. with the size of their van der Waals radii.) Some authors in the DEM community employ the term MD rather loosely, even when their simulations do not model actual molecules.

Design Constraints

Design of a molecular dynamics simulation should account for the available computational power. Simulation size (n=number of particles), timestep and total time duration must be selected so that the calculation can finish within a reasonable time period. However, the simulations should be long enough to be relevant to the time scales of the natural processes being studied. To make statistically valid conclusions from the simulations, the time span simulated should match the kinetics of the natural process. Otherwise, it is analogous to making conclusions about how a human walks from less than one footstep. Most scientific publications about the dynamics of proteins and DNA use data from simulations spanning nanoseconds (1E-9 s) to microseconds (1E-6 s). To obtain these simulations, several CPU-days to CPU-years are needed. Parallel algorithms allow the load to be distributed among CPUs; an example is the spatial decomposition in LAMMPS.

During a classical MD simulation, the most CPU intensive task is the evaluation of the potential (force field) as a function of the particles' internal coordinates. Within that energy evaluation, the most expensive one is the non-bonded or non-covalent part. In Big O notation, common molecular dynamics simulations scale by $O(n^2)$ if all pair-wise electrostatic and van der Waals interactions must be accounted for explicitly. This computational cost can be reduced by employing electrostatics methods such as Particle Mesh Ewald ($O(n \log(n))$) or good spherical cutoff techniques ($O(n)$).

Another factor that impacts total CPU time required by a simulation is the size of the integration timestep. This is the time length between evaluations of the potential. The timestep must be chosen small enough to avoid discretization errors (i.e. smaller than the fastest vibrational frequency in the system). Typical timesteps for classical MD are in the order of 1 femtosecond (1E-15 s). This value may be extended by using algorithms such as SHAKE, which fix the vibrations of the fastest atoms (e.g. hydrogens) into place. Multiple time scale methods have also been developed, which allow for extended times between updates of slower long-range forces.[6] [7] [8]

For simulating molecules in a solvent, a choice should be made between explicit solvent and implicit solvent. Explicit solvent particles (such as the TIP3P and SPC/E water models) must be calculated expensively by the force field, while implicit solvents use a mean-field approach. Using an explicit solvent is computationally expensive, requiring inclusion of about ten times more particles in the simulation. But the granularity and viscosity of explicit solvent is essential to reproduce certain properties of the solute molecules. This is especially important to reproduce kinetics.

In all kinds of molecular dynamics simulations, the simulation box size must be large enough to avoid boundary condition artifacts. Boundary conditions are often treated by choosing fixed values at the edges, or by employing periodic boundary conditions in which one side of the simulation loops back to the opposite side, mimicking a bulk phase.

Microcanonical ensemble (NVE)

In the **microcanonical**, or **NVE** ensemble, the system is isolated from changes in moles (N), volume (V) and energy (E). It corresponds to an adiabatic process with no heat exchange. A microcanonical molecular dynamics trajectory may be seen as an exchange of potential and kinetic energy, with total energy being conserved. For a system of N particles with coordinates X and velocities V, the following pair of first order differential equations may be written in Newton's notation as

$$F(X) = -\nabla U(X) = M\dot{V}(t)$$
$$V(t) = \dot{X}(t).$$

The potential energy function $U(X)$ of the system is a function of the particle coordinates X. It is referred to simply as the "potential" in Physics, or the "force field" in Chemistry. The first equation comes from Newton's laws; the force F acting on each particle in the system can be calculated as the negative gradient of $U(X)$.

For every timestep, each particle's position X and velocity V may be integrated with a symplectic method such as Verlet. The time evolution of X and V is called a trajectory. Given the initial positions (e.g. from theoretical knowledge) and velocities (e.g. randomized Gaussian), we can calculate all future (or past) positions and velocities.

One frequent source of confusion is the meaning of temperature in MD. Commonly we have experience with macroscopic temperatures, which involve a huge number of particles. But temperature is a statistical quantity. If there is a large enough number of atoms, statistical temperature can be estimated from the *instantaneous temperature*, which is found by equating the kinetic energy of the system to $nk_BT/2$ where n is the number of degrees of freedom of the system.

A temperature-related phenomenon arises due to the small number of atoms that are used in MD simulations. For example, consider simulating the growth of a copper film starting with a substrate containing 500 atoms and a deposition energy of 100 eV. In the real world, the 100 eV from the deposited atom would rapidly be transported through and shared among a large number of atoms (10^{10} or more) with no big change in temperature. When there are only 500 atoms, however, the substrate is almost immediately vaporized by the deposition. Something similar happens in biophysical simulations. The temperature of the system in NVE is naturally raised when macromolecules such as proteins undergo exothermic conformational changes and binding.

Canonical ensemble (NVT)

In the canonical ensemble, moles (N), volume (V) and temperature (T) are conserved. It is also sometimes called constant temperature molecular dynamics (CTMD). In NVT, the energy of endothermic and exothermic processes is exchanged with a thermostat.

A variety of thermostat methods are available to add and remove energy from the boundaries of an MD system in a realistic way, approximating the canonical ensemble. Popular techniques to control temperature include the Nosé-Hoover thermostat, the Berendsen thermostat, and Langevin dynamics. Note that the Berendsen thermostat might introduce the flying ice cube effect, which leads to unphysical translations and rotations of the simulated system.

Isothermal-Isobaric (NPT) ensemble

In the isothermal-isobaric ensemble, moles (N), pressure (P) and temperature (T) are conserved. In addition to a thermostat, a barostat is needed. It corresponds most closely to laboratory conditions with a flask open to ambient temperature and pressure.

In the simulation of biological membranes, isotropic pressure control is not appropriate. For lipid bilayers, pressure control occurs under constant membrane area (NPAT) or constant surface tension "gamma" (NPγT).

Generalized ensembles

The replica exchange method is a generalized ensemble. It was originally created to deal with the slow dynamics of disordered spin systems. It is also called parallel tempering. The replica exchange MD (REMD) formulation [9] tries to overcome the multiple-minima problem by exchanging the temperature of non-interacting replicas of the system running at several temperatures.

Potentials in MD simulations

A molecular dynamics simulation requires the definition of a potential function, or a description of the terms by which the particles in the simulation will interact. In chemistry and biology this is usually referred to as a force field. Potentials may be defined at many levels of physical accuracy; those most commonly used in chemistry are based on molecular mechanics and embody a classical treatment of particle-particle interactions that can reproduce structural and conformational changes but usually cannot reproduce chemical reactions.

The reduction from a fully quantum description to a classical potential entails two main approximations. The first one is the Born-Oppenheimer approximation, which states that the dynamics of electrons is so fast that they can be considered to react instantaneously to the motion of their nuclei. As a consequence, they may be treated separately. The second one treats the nuclei, which are much heavier than electrons, as point particles that follow classical Newtonian dynamics. In classical molecular dynamics the effect of the electrons is approximated as a single potential energy surface, usually representing the ground state.

When finer levels of detail are required, potentials based on quantum mechanics are used; some techniques attempt to create hybrid classical/quantum potentials where the bulk of the system is treated classically but a small region is treated as a quantum system, usually undergoing a chemical transformation.

Empirical potentials

Empirical potentials used in chemistry are frequently called force fields, while those used in materials physics are called just empirical or analytical potentials.

Most force fields in chemistry are empirical and consist of a summation of bonded forces associated with chemical bonds, bond angles, and bond dihedrals, and non-bonded forces associated with van der Waals forces and electrostatic charge. Empirical potentials represent quantum-mechanical effects in a limited way through ad-hoc functional approximations. These potentials contain free parameters such as atomic charge, van der Waals parameters reflecting estimates of atomic radius, and equilibrium bond length, angle, and dihedral; these are obtained by fitting against detailed electronic calculations

(quantum chemical simulations) or experimental physical properties such as elastic constants, lattice parameters and spectroscopic measurements.

Because of the non-local nature of non-bonded interactions, they involve at least weak interactions between all particles in the system. Its calculation is normally the bottleneck in the speed of MD simulations. To lower the computational cost, force fields employ numerical approximations such as shifted cutoff radii, reaction field algorithms, particle mesh Ewald summation, or the newer Particle-Particle Particle Mesh (P3M).

Chemistry force fields commonly employ preset bonding arrangements (an exception being *ab-initio* dynamics), and thus are unable to model the process of chemical bond breaking and reactions explicitly. On the other hand, many of the potentials used in physics, such as those based on the bond order formalism can describe several different coordinations of a system and bond breaking. Examples of such potentials include the Brenner potential[10] for hydrocarbons and its further developments for the C-Si-H and C-O-H systems. The ReaxFF potential[11] can be considered a fully reactive hybrid between bond order potentials and chemistry force fields.

Pair potentials vs. many-body potentials

The potential functions representing the non-bonded energy are formulated as a sum over interactions between the particles of the system. The simplest choice, employed in many popular force fields, is the "pair potential", in which the total potential energy can be calculated from the sum of energy contributions between pairs of atoms. An example of such a pair potential is the non-bonded Lennard-Jones potential (also known as the 6-12 potential), used for calculating van der Waals forces.

$$U(r) = 4\varepsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^{6} \right]$$

Another example is the Born (ionic) model of the ionic lattice. The first term in the next equation is Coulomb's law for a pair of ions, the second term is the short-range repulsion explained by Pauli's exclusion principle and the final term is the dispersion interaction term. Usually, a simulation only includes the dipolar term, although sometimes the quadrupolar term is included as well.

$$U_{ij}(r_{ij}) = \sum \frac{z_i z_j}{4\pi\epsilon_0} \frac{1}{r_{ij}} + \sum A_l \exp \frac{-r_{ij}}{p_l} + \sum C_l r_{ij}^{-n_j} + \cdots$$

In many-body potentials, the potential energy includes the effects of three or more particles interacting with each other. In simulations with pairwise potentials, global interactions in the system also exist, but they occur only through pairwise terms. In many-body potentials, the potential energy cannot be found by a sum over pairs of atoms, as these interactions are calculated explicitly as a combination of higher-order terms. In the statistical view, the dependency between the variables cannot in general be expressed using only pairwise products of the degrees of freedom. For example, the Tersoff potential[12], which was originally used to simulate carbon, silicon and germanium and has since been used for a wide range of other materials, involves a sum over groups of three atoms, with the angles between the atoms being an important factor in the potential. Other examples are the embedded-atom method (EAM)[13] and the Tight-Binding Second Moment Approximation (TBSMA) potentials[14], where the electron density of states in the region of an atom is calculated from a sum of contributions from surrounding atoms, and the potential energy contribution is then a function of this sum.

Semi-empirical potentials

Semi-empirical potentials make use of the matrix representation from quantum mechanics. However, the values of the matrix elements are found through empirical formulae that estimate the degree of overlap of specific atomic orbitals. The matrix is then diagonalized to determine the occupancy of the different atomic orbitals, and empirical formulae are used once again to determine the energy contributions of the orbitals.

There are a wide variety of semi-empirical potentials, known as tight-binding potentials, which vary according to the atoms being modeled.

Polarizable potentials

Most classical force fields implicitly include the effect of polarizability, e.g. by scaling up the partial charges obtained from quantum chemical calculations. These partial charges are stationary with respect to the mass of the atom. But molecular dynamics simulations can explicitly model polarizability with the introduction of induced dipoles through different methods, such as Drude particles or fluctuating charges. This allows for a dynamic redistribution of charge between atoms which responds to the local chemical environment.

For many years, polarizable MD simulations have been touted as the next generation. For homogenous liquids such as water, increased accuracy has been achieved through the inclusion of polarizability.[15] Some promising results have also been achieved for proteins.[16] However, it is still uncertain how to best approximate polarizability in a simulation.

Ab-initio methods

In classical molecular dynamics, a single potential energy surface (usually the ground state) is represented in the force field. This is a consequence of the Born-Oppenheimer approximation. If excited states, chemical reactions or a more accurate representation is needed, electronic behavior can be obtained from first principles by using a quantum mechanical method, such as Density Functional Theory. This is known as Ab Initio Molecular Dynamics (AIMD). Due to the cost of treating the electronic degrees of freedom, the computational cost of this simulations is much higher than classical molecular dynamics. This implies that AIMD is limited to smaller systems and shorter periods of time.

Ab-initio quantum-mechanical methods may be used to calculate the potential energy of a system on the fly, as needed for conformations in a trajectory. This calculation is usually made in the close neighborhood of the reaction coordinate. Although various approximations may be used, these are based on theoretical considerations, not on empirical fitting. *Ab-Initio* calculations produce a vast amount of information that is not available from empirical methods, such as density of electronic states or other electronic properties. A significant advantage of using *ab-initio* methods is the ability to study reactions that involve breaking or formation of covalent bonds, which correspond to multiple electronic states.

A popular software for *ab-initio* molecular dynamics is the Car-Parrinello Molecular Dynamics (CPMD) package based on the density functional theory.

Hybrid QM/MM

QM (quantum-mechanical) methods are very powerful. However, they are computationally expensive, while the MM (classical or molecular mechanics) methods are fast but suffer from several limitations (require extensive parameterization; energy estimates obtained are not very accurate; cannot be used to simulate reactions where covalent bonds are broken/formed; and are limited in their abilities for providing accurate details regarding the chemical environment). A new class of method has emerged that combines the good points of QM (accuracy) and MM (speed) calculations. These methods are known as mixed or hybrid quantum-mechanical and molecular mechanics methods (hybrid QM/MM). The methodology for such techniques was introduced by Warshel and coworkers. In the recent years have been pioneered by several groups including: Arieh Warshel (University of Southern California), Weitao Yang (Duke University), Sharon Hammes-Schiffer (The Pennsylvania State University), Donald Truhlar and Jiali Gao (University of Minnesota) and Kenneth Merz (University of Florida).

The most important advantage of hybrid QM/MM methods is the speed. The cost of doing classical molecular dynamics (MM) in the most straightforward case scales $O(n^2)$, where N is the number of atoms in the system. This is mainly due to electrostatic interactions term (every particle interacts with every other particle). However, use of cutoff radius, periodic pair-list updates and more recently the variations of the particle-mesh Ewald's (PME) method has reduced this between $O(N)$ to $O(n^2)$. In other words, if a system with twice many atoms is simulated then it would take between twice to four times as much computing power. On the other hand the simplest *ab-initio* calculations typically scale $O(n^3)$ or worse (Restricted Hartree-Fock calculations have been suggested to scale $\sim O(n^{2.7})$). To overcome the limitation, a small part of the system is treated quantum-mechanically (typically active-site of an enzyme) and the remaining system is treated classically.

In more sophisticated implementations, QM/MM methods exist to treat both light nuclei susceptible to quantum effects (such as hydrogens) and electronic states. This allows generation of hydrogen wave-functions (similar to electronic wave-functions). This methodology has been useful in investigating phenomenon such as hydrogen tunneling. One example where QM/MM methods have provided new discoveries is the calculation of hydride transfer in the enzyme liver alcohol dehydrogenase. In this case, tunneling is important for the hydrogen, as it determines the reaction rate.[17]

Coarse-graining and reduced representations

At the other end of the detail scale are coarse-grained and lattice models. Instead of explicitly representing every atom of the system, one uses "pseudo-atoms" to represent groups of atoms. MD simulations on very large systems may require such large computer resources that they cannot easily be studied by traditional all-atom methods. Similarly, simulations of processes on long timescales (beyond about 1 microsecond) are prohibitively expensive, because they require so many timesteps. In these cases, one can sometimes tackle the problem by using reduced representations, which are also called coarse-grained models.

Examples for coarse graining (CG) methods are discontinuous molecular dynamics (CG-DMD)[18] [19] and Go-models[20] . Coarse-graining is done sometimes taking larger pseudo-atoms. Such united atom approximations have been used in MD simulations of biological membranes. The aliphatic tails of lipids are represented by a few pseudo-atoms

by gathering 2-4 methylene groups into each pseudo-atom.

The parameterization of these very coarse-grained models must be done empirically, by matching the behavior of the model to appropriate experimental data or all-atom simulations. Ideally, these parameters should account for both enthalpic and entropic contributions to free energy in an implicit way. When coarse-graining is done at higher levels, the accuracy of the dynamic description may be less reliable. But very coarse-grained models have been used successfully to examine a wide range of questions in structural biology.

Examples of applications of coarse-graining in biophysics:

- protein folding studies are often carried out using a single (or a few) pseudo-atoms per amino acid;
- DNA supercoiling has been investigated using 1-3 pseudo-atoms per basepair, and at even lower resolution;
- Packaging of double-helical DNA into bacteriophage has been investigated with models where one pseudo-atom represents one turn (about 10 basepairs) of the double helix;
- RNA structure in the ribosome and other large systems has been modeled with one pseudo-atom per nucleotide.

The simplest form of coarse-graining is the "united atom" (sometimes called "extended atom") and was used in most early MD simulations of proteins, lipids and nucleic acids. For example, instead of treating all four atoms of a CH_3 methyl group explicitly (or all three atoms of CH_2 methylene group), one represents the whole group with a single pseudo-atom. This pseudo-atom must, of course, be properly parameterized so that its van der Waals interactions with other groups have the proper distance-dependence. Similar considerations apply to the bonds, angles, and torsions in which the pseudo-atom participates. In this kind of united atom representation, one typically eliminates all explicit hydrogen atoms except those that have the capability to participate in hydrogen bonds ("polar hydrogens"). An example of this is the Charmm 19 force-field.

The polar hydrogens are usually retained in the model, because proper treatment of hydrogen bonds requires a reasonably accurate description of the directionality and the electrostatic interactions between the donor and acceptor groups. A hydroxyl group, for example, can be both a hydrogen bond donor and a hydrogen bond acceptor, and it would be impossible to treat this with a single OH pseudo-atom. Note that about half the atoms in a protein or nucleic acid are nonpolar hydrogens, so the use of united atoms can provide a substantial savings in computer time.

Examples of applications

Molecular dynamics is used in many fields of science.

- First macromolecular MD simulation published (1977, Size: 500 atoms, Simulation Time: 9.2 ps=0.0092 ns, Program: CHARMM precursor) Protein: Bovine Pancreatic Trypsine Inhibitor. This is one of the best studied proteins in terms of folding and kinetics. Its simulation published in Nature magazine paved the way for understanding protein motion as essential in function and not just accessory.[21]
- MD is the standard method to treat collision cascades in the heat spike regime, i.e. the effects that energetic neutron and ion irradiation have on solids an solid surfaces.[22] [23]

The following two biophysical examples are not run-of-the-mill MD simulations. They illustrate almost heroic efforts to produce simulations of a system of very large size (a complete virus) and very long simulation times (500 microseconds):

- MD simulation of the complete satellite tobacco mosaic virus (**STMV**) (2006, Size: 1 million atoms, Simulation time: 50 ns, program: NAMD) This virus is a small, icosahedral plant virus which worsens the symptoms of infection by Tobacco Mosaic Virus (TMV). Molecular dynamics simulations were used to probe the mechanisms of viral assembly. The entire STMV particle consists of 60 identical copies of a single protein that make up the viral capsid (coating), and a 1063 nucleotide single stranded RNA genome. One key finding is that the capsid is very unstable when there is no RNA inside. The simulation would take a single 2006 desktop computer around 35 years to complete. It was thus done in many processors in parallel with continuous communication between them.[24]

- Folding Simulations of the Villin Headpiece in All-Atom Detail (2006, Size: 20,000 atoms; Simulation time: 500 μs = 500,000 ns, Program: folding@home) This simulation was run in 200,000 CPU's of participating personal computers around the world. These computers had the folding@home program installed, a large-scale distributed computing effort coordinated by Vijay Pande at Stanford University. The kinetic properties of the Villin Headpiece protein were probed by using many independent, short trajectories run by CPU's without continuous real-time communication. One technique employed was the Pfold value analysis, which measures the probability of folding before unfolding of a specific starting conformation. Pfold gives information about transition state structures and an ordering of conformations along the folding pathway. Each trajectory in a Pfold calculation can be relatively short, but many independent trajectories are needed.[25]

Molecular dynamics algorithms

Integrators
- Verlet-Stoermer integration
- Runge-Kutta integration
- Beeman's algorithm
- Gear predictor - corrector
- Constraint algorithms (for constrained systems)
- Symplectic integrator

Short-range interaction algorithms
- Cell lists
- Verlet list
- Bonded interactions

Long-range interaction algorithms
- Ewald summation
- Particle Mesh Ewald (PME)
- Particle-Particle Particle Mesh P3M
- Reaction Field Method

Parallelization strategies

- Domain decomposition method (Distribution of system data for parallel computing)
- Molecular Dynamics - Parallel Algorithms [26]

Major software for MD simulations

- Abalone (classical, implicit water)
- ABINIT (DFT)
- ACEMD [27] (running on NVIDIA GPUs: heavily optimized with CUDA)
- ADUN [28] (classical, P2P database for simulations)
- AMBER (classical)
- Ascalaph [29] (classical, GPU accelerated)
- CASTEP (DFT)
- CPMD (DFT)
- CP2K [30] (DFT)
- CHARMM (classical, the pioneer in MD simulation, extensive analysis tools)
- COSMOS [31] (classical and hybrid QM/MM, quantum-mechanical atomic charges with BPT)
- Desmond [32] (classical, parallelization with up to thousands of CPU's)
- DL_POLY [33] (classical)
- ESPResSo (classical, coarse-grained, parallel, extensible)
- Fireball [34] (tight-binding DFT)
- GROMACS (classical)
- GROMOS (classical)
- GULP (classical)
- Hippo [35] (classical)
- LAMMPS (classical, large-scale with spatial-decomposition of simulation domain for parallelism)
- MDynaMix (classical, parallel)
- MOLDY [36] (classical, parallel) latest release [37]
- Materials Studio [38] (Forcite MD using COMPASS, Dreiding, Universal, cvff and pcff forcefields in serial or parallel, QMERA (QM+MD), ONESTEP (DFT), etc.)
- MOSCITO (classical)
- NAMD (classical, parallelization with up to thousands of CPU's)
- NEWTON-X [39] (ab initio, surface-hopping dynamics)
- ProtoMol [40] (classical, extensible, includes multigrid electrostatics)
- PWscf (DFT)
- S/PHI/nX [41] (DFT)
- SIESTA (DFT)
- VASP (DFT)
- TINKER (classical)
- YASARA [42] (classical)
- ORAC [43] (classical)
- XMD (classical)

Related software

- VMD - MD simulation trajectories can be visualized and analyzed.
- PyMol - Molecular Visualization software written in python
- Packmol [44] Package for building starting configurations for MD in an automated fashion
- Sirius - Molecular modeling, analysis and visualization of MD trajectories
- esra [45] - Lightweight molecular modeling and analysis library (Java/Jython/Mathematica).
- Molecular Workbench [46] - Interactive molecular dynamics simulations on your desktop
- BOSS - MC in OPLS

Specialized hardware for MD simulations

- Anton - A specialized, massively parallel supercomputer designed to execute MD simulations.
- MDGRAPE - A special purpose system built for molecular dynamics simulations, especially protein structure prediction.

See also

- Molecular graphics
- Molecular modeling
- Computational chemistry
- Energy drift
- Force field in Chemistry
- Force field implementation
- Monte Carlo method
- Molecular Design software
- Molecular mechanics
- Molecular modeling on GPU
- Protein dynamics
- Implicit solvation
- Car-Parrinello method
- Symplectic numerical integration
- Software for molecular mechanics modeling
- Dynamical systems
- Theoretical chemistry
- Statistical mechanics
- Quantum chemistry
- Discrete element method
- List of nucleic acid simulation software

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[32] http://www.DEShawResearch.com/resources.html

[33] http://www.ccp5.ac.uk/DL_POLY/

[34] http://fireball-dft.org

[35] http://www.biowerkzeug.com/

[36] http://www.ccp5.ac.uk/moldy/moldy.html

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[38] http://accelrys.com/products/materials-studio/

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External links

- The Blue Gene Project (http://researchweb.watson.ibm.com/bluegene/) (IBM)
- D. E. Shaw Research (http://deshawresearch.com/) (D. E. Shaw Research)
- Molecular Physics (http://www.tandf.co.uk/journals/titles/00268976.asp)
- Statistical mechanics of Nonequilibrium Liquids (http://www.phys.unsw.edu.au/~gary/book.html) Lecture Notes on non-equilibrium MD
- Introductory Lecture on Classical Molecular Dynamics (http://www.fz-juelich.de/nic-series/volume10/sutmann.pdf) by Dr. Godehard Sutmann, NIC, Forschungszentrum Jülich, Germany
- Introductory Lecture on Ab Initio Molecular Dynamics and Ab Initio Path Integrals (http://www.fz-juelich.de/nic-series/volume10/tuckerman2.pdf) by Mark E. Tuckerman, New York University, USA
- Introductory Lecture on Ab initio molecular dynamics: Theory and Implementation (http://www.fz-juelich.de/nic-series/Volume1/marx.pdf) by Dominik Marx, Ruhr-Universität Bochum and Jürg Hutter, Universität Zürich

Computer model

1. REDIRECT Computer simulation

Quantum Monte Carlo

Electronic structure methods
Tight binding
Nearly-free electron model
Hartree–Fock
Modern valence bond
Generalized valence bond
Møller–Plesset perturbation theory
Configuration interaction
Coupled cluster
Multi-configurational self-consistent field
Density functional theory
Quantum chemistry composite methods
Quantum Monte Carlo
k·p perturbation theory
Muffin-tin approximation
LCAO method

Quantum Monte Carlo is a large class of computer algorithms that simulate quantum systems with the idea of solving the many-body problem. They use, in one way or another, the Monte Carlo method to handle the many-dimensional integrals that arise. Quantum

Monte Carlo allows a direct representation of many-body effects in the wavefunction, at the cost of statistical uncertainty that can be reduced with more simulation time. For bosons, there exist numerically exact and polynomial-scaling algorithms. For fermions, there exist very good approximations and numerically exact exponentially scaling quantum Monte Carlo algorithms, but none that are both.

Background

In principle, any physical system can be described by the many-body Schrödinger equation as long as the constituent particles are not moving "too" fast; that is, they are not moving near the speed of light. This includes the electrons in almost every material in the world, so if we could solve the Schrödinger equation, we could predict the behavior of any electronic system, which has important applications in fields from computers to biology. This also includes the nuclei in Bose–Einstein condensate and superfluids such as liquid helium. The difficulty is that the Schrödinger equation involves a function of three times the number of particles and is difficult to solve even using parallel computing technology in a reasonable amount of time (less than 2 years). Traditionally, theorists have approximated the many-body wave function as an antisymmetric function of one-body orbitals, as shown concisely at this link.[1] This kind of formulation either limits the possible wave functions, as in the case of the Hartree-Fock (HF) approximation, or converges very slowly, as in configuration interaction. One of the reasons for the difficulty with an HF initial estimate (ground state seed, also known as Slater determinant) is that it is very difficult to model the electronic and nuclear cusps in the wavefunction. However, one does not generally model at this point of the approximation. As two particles approach each other, the wavefunction has exactly known derivatives.

Quantum Monte Carlo is a way around these problems because it allows us to model a many-body wavefunction of our choice directly. Specifically, we can use a Hartree-Fock approximation as our starting point but then multiplying it by any symmetric function, of which Jastrow functions are typical, designed to enforce the cusp conditions. Most methods aim at computing the ground-state wavefunction of the system, with the exception of path integral Monte Carlo and finite-temperature auxiliary field Monte Carlo, which calculate the density matrix.

There are several quantum Monte Carlo methods, each of which uses Monte Carlo in different ways to solve the many-body problem:

Quantum Monte Carlo methods

- Stochastic Green function (SGF) algorithm : An algorithm designed for bosons that can simulate any complicated lattice Hamiltonian that does not have a sign problem. Used in combination with a directed update scheme, this is a powerful tool.
- Variational Monte Carlo : A good place to start; it is commonly used in many sorts of quantum problems.
- Diffusion Monte Carlo : The most common high-accuracy method for electrons (that is, chemical problems), since it comes quite close to the exact ground-state energy fairly efficiently. Also used for simulating the quantum behavior of atoms, etc.
- Path integral Monte Carlo : Finite-temperature technique mostly applied to bosons where temperature is very important, especially superfluid helium.

- Auxiliary field Monte Carlo : Usually applied to lattice problems, although there has been recent work on applying it to electrons in chemical systems.
- Reptation Monte Carlo : Recent zero-temperature method related to path integral Monte Carlo, with applications similar to diffusion Monte Carlo but with some different tradeoffs.
- Gaussian quantum Monte Carlo

See also

- Stochastic Green Function (SGF) algorithm
- Monte Carlo method
- QMC@Home
- Quantum chemistry
- Density matrix renormalization group
- Time-evolving block decimation
- Metropolis algorithm
- Wavefunction optimization

Implementations

- ALPS [2]
- CASINO [3]
- CHAMP [4]
- Monte Python [5]
- PIMC++ [6]
- pi-qmc [7]
- QMcBeaver [8]
- QmcMol [9]
- QMCPACK [10]
- Qumax [11]
- Qwalk [12]
- TurboRVB [13]
- Zori [14]

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[4] http://pages.physics.cornell.edu/~cyrus/champ.html
[5] http://code.google.com/p/montepython/
[6] http://cms.mcc.uiuc.edu/pimcpp/
[7] http://code.google.com/p/pi-qmc/
[8] http://qmcbeaver.sourceforge.net/
[9] http://www.lct.jussieu.fr/pagesequipe/qmcmol/qmcmol/
[10] http://www.mcc.uiuc.edu/qmc/qmcpack/index.html
[11] http://attaccalite.altervista.org/qumax/index.php
[12] http://www.qwalk.org/
[13] http://turborvb.qe-forge.org
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External links

- QMCWIKI (http://www.qmcwiki.org/)
- Joint DEMOCRITOS-ICTP School on Continuum Quantum Monte Carlo Methods (http://cdsagenda5.ictp.trieste.it/full_display.php?ida=a0332&fid=)
- FreeScience Library -> Quantum Monte Carlo (http://freescience.info/books.php?id=35)
- UIUC 2007 Summer School on Computational Materials Science: Quantum Monte Carlo from Minerals and Materials to Molecules (http://www.mcc.uiuc.edu/summerschool/2007/qmc/)
- Quantum Monte Carlo in the Apuan Alps V (http://www.vallico.net/tti/tti.html) - international workshop, Vallico Sotto, Tuscany, 25 July-1 August 2009 (Click PUBLIC EVENTS) - Announcement (http://www.vallico.net/tti/qmcitaa_09/announcement.html), Poster (http://www.tcm.phy.cam.ac.uk/~mdt26/tti2/poster/tti_c_poster_2009.png)
- Quantum Monte Carlo and the CASINO program IV (http://www.vallico.net/tti/tti.html) - summer school, Vallico Sotto, Tuscany, 2-9 August 2009 (Click PUBLIC EVENTS) - Announcement (http://www.vallico.net/tti/qmcatcp_09/announcement.html), Poster (http://www.tcm.phy.cam.ac.uk/~mdt26/tti2/poster/tti_ss_poster_2009.png)

Molecular graphics

Molecular graphics (**MG**) is the discipline and philosophy of studying molecules and their properties through graphical representation.[1] IUPAC limits the definition to representations on a "graphical display device".[2] Ever since Dalton's atoms and Kekule's benzene, there has been a rich history of hand-drawn atoms and molecules, and these representations have had an important influence on modern molecular graphics. This article concentrates on the use of computers to create molecular graphics. Note, however, that many molecular graphics programs and systems have close coupling between the graphics and editing commands or calculations such as in molecular modelling.

Relation to molecular models

There has been a long tradition of creating molecular models from physical materials. Perhaps the best known is Crick and Watson's model of DNA built from rods and planar sheets, but the most widely used approach is to represent all atoms and bonds explicitly using the "ball and stick" approach. This can demonstrate a wide range of properties, such as shape, relative size, and flexibility. Many chemistry courses expect that students will have access to ball and stick models. One goal of mainstream molecular graphics has been to represent the "ball and stick" model as realistically as possible and to couple this with calculations of molecular properties.
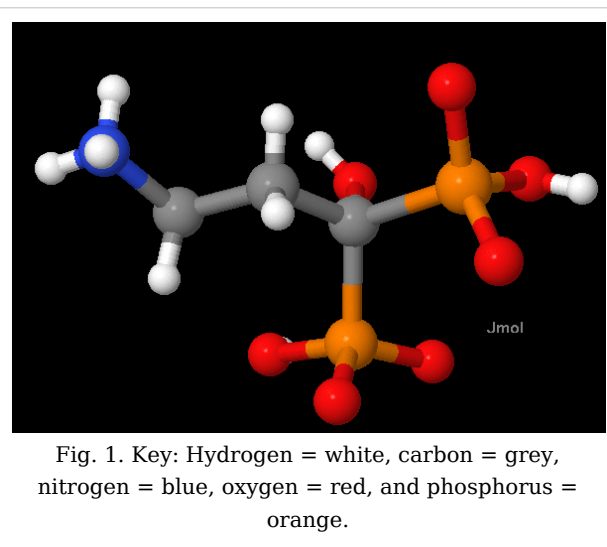
Fig. 1. Key: Hydrogen = white, carbon = grey, nitrogen = blue, oxygen = red, and phosphorus = orange.

Figure 1 shows a small molecule ($NH_3CH_2CH_2C(OH)(PO_3H)(PO_3H)$-), as drawn by the Jmol program. It is important to realise that the colours are purely a convention. Molecules can never be visible under any light microscope and atoms are not coloured, do not have hard surfaces and do not reflect light. Bonds are not rod-shaped. If physical molecular models had not existed, it is unlikely that molecular graphics would currently use this metaphor.

Comparison of physical models with molecular graphics

Physical models and computer models have partially complementary strengths and weaknesses. Physical models can be used by those without access to a computer and now can be made cheaply out of plastic materials. Their tactile and visual aspects cannot be easily reproduced by computers (although haptic devices have occasionally been built). On a computer screen, the flexibility of molecules is also difficult to appreciate; illustrating the pseudorotation of cyclohexane is a good example of the value of mechanical models.

However, it is difficult to build large physical molecules, and all-atom physical models of even simple proteins could take weeks or months to build. Moreover, physical models are not robust and they decay over time. Molecular graphics is particularly valuable for representing global and local properties of molecules, such as electrostatic potential.

Graphics can also be animated to represent molecular processes and chemical reactions, a feat that is not easy to reproduce physically.

History

Initially the rendering was on early CRT screens or through plotters drawing on paper. Molecular structures have always been an attractive choice for developing new computer graphics tools, since the input data are easy to create and the results are usually highly appealing. The first example of MG was a display of a protein molecule (Project MAC, 1966) by Cyrus Levinthal and Robert Langridge. Among the milestones in high-performance MG was the work of Nelson Max in "realistic" rendering of macromolecules using reflecting spheres.

By about 1980 many laboratories both in academia and industry had recognized the power of the computer to analyse and predict the properties of molecules, especially in materials science and the pharmaceutical industry. The discipline was often called "molecular graphics" and in 1982 a group of academics and industrialists in the UK set up the Molecular Graphics Society (MGS). Initially much of the technology concentrated either on high-performance 3D graphics, including interactive rotation or 3D rendering of atoms as spheres (sometimes with radiosity). During the 1980s a number of programs for calculating molecular properties (such as molecular dynamics and quantum mechanics) became available and the term "molecular graphics" often included these. As a result the MGS has now changed its name to the Molecular Graphics and Modelling Society (MGMS).

The requirements of macromolecular crystallography also drove MG because the traditional techniques of physical model-building could not scale. Alwyn Jones' FRODO program (and later "O") were developed to overlay the molecular electron density determined from X-ray crystallography and the hypothetical molecular structure.

Art, science and technology in molecular graphics

Both computer technology and graphic arts have contributed to molecular graphics. The development of structural biology in the 1950s led to a requirement to display molecules with thousands of atoms. The existing computer technology was limited in power, and in any case a naive depiction of all atoms left viewers overwhelmed. Most systems therefore used conventions where information was implicit or stylistic. Two vectors meeting at a point implied an atom or (in macromolecules) a complete residue (10-20 atoms).

The macromolecular approach was popularized by Dickerson and Geis' presentation of proteins and the graphic work of Jane Richardson through high-quality hand-drawn diagrams such as the "ribbon" representation. In this they strove to capture the intrinsic 'meaning' of the molecule. This search for the "messages in the molecule" has always accompanied the increasing power of computer graphics processing. Typically the depiction would concentrate on specific areas of the molecule (such as the active site) and this might have different colours or more detail in the number of explicit atoms or the type of depiction (e.g., spheres for atoms).

Fig. 2. Image of hemagglutinin with alpha helices depicted as cylinders and the rest of the chain as silver coils. The individual protein atoms (several thousand) have been hidden. All of the non-hydrogen atoms in the two ligands (presumably sialic acid) have been shown near the top of the diagram. Key: Carbon = grey, oxygen = red, nitrogen = blue.

In some cases the limitations of technology have led to serendipitous methods for rendering. Most early graphics devices used vector graphics, which meant that rendering spheres and surfaces was impossible. Michael Connolly's program "MS" calculated points on the surface-accessible surface of a molecule, and the points were rendered as dots with good visibility using the new vector graphics technology, such as the Evans and Sutherland PS300 series. Thin sections ("slabs") through the structural display showed very clearly the complementarity of the surfaces for molecules binding to active sites, and the "Connolly surface" became a universal metaphor.

The relationship between the art and science of molecular graphics is shown in the exhibitions [3] sponsored by the Molecular Graphics Society. Some exhibits are created with molecular graphics programs alone, while others are collages, or involve physical materials. An example from Mike Hann (1994), inspired by Magritte's painting *Ceci n'est pas une pipe*, uses an image of a salmeterol molecule.

"*Ceci n'est pas une molecule*," writes Mike Hann, "serves to remind us that all of the graphics images presented here are not molecules, not even pictures of molecules, but pictures of icons which we believe represent some aspects of the molecule's properties."

Space-filling models

Fig. 4 is a "space-filling" representation of formic acid, where atoms are drawn to suggest the amount of space they occupy. This is necessarily an icon: in the quantum mechanical representation of molecules, there are only (positively charged) nuclei and a "cloud" of negative electrons. The electron cloud defines an approximate size for the molecule, though there can be no single precise definition of size. For many years the size of atoms has been approximated by mechanical models (CPK), where the atoms have been represented by plastic spheres whose radius (van der Waals radius) describes a sphere within which "most" of the electron density can be found. These spheres could be clicked together to show the steric aspects of the molecule rather than the positions of the nuclei. Fig. 4 shows the

Fig. 4. Space-filling model of formic acid. Key: Hydrogen = white, carbon = black, oxygen = red.

intricacy required to make sure that all spheres intersect correctly, and also demonstrates a reflective model.

Fig. 5. A molecule (zirconocene) where part (left) is rendered as ball-and-stick and part (right) as an isosurface.
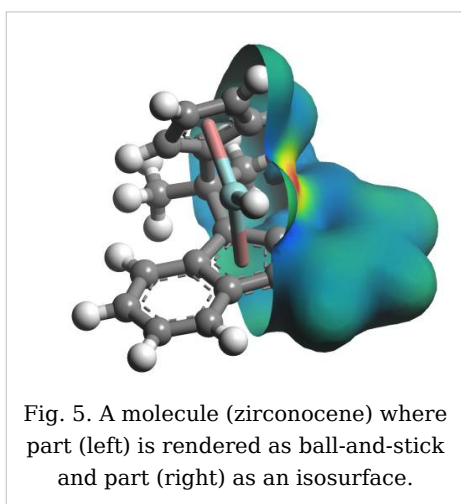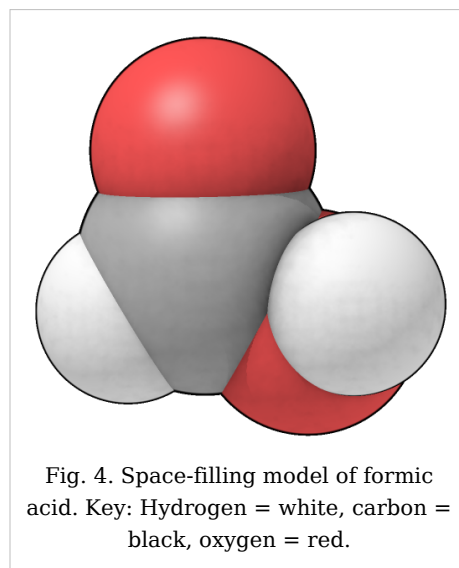
Since the atomic radii (e.g. in Fig. 4) are only slightly less than the distance between bonded atoms, the iconic spheres intersect, and in the CPK models, this was achieved by planar truncations along the bonding directions, the section being circular. When raster graphics became affordable, one of the common approaches was to replicate CPK models *in silico*. It is relatively straightforward to calculate the circles of intersection, but more complex to represent a model with hidden surface removal. A useful side product is that a conventional value for the molecular volume can be calculated.

The use of spheres is often for convenience, being limited both by graphics libraries and the additional effort required to compute complete electronic density or other space-filling quantities. It is now relatively common to see images of isosurfaces that have been coloured to show quantities such as electrostatic potential. The commonest isosurfaces are the Connolly surface, or the volume within which a given proportion of the electron density lies. The isosurface in Fig. 5 appears to show the electrostatic potential, with blue colours being negative and red/yellow (near the metal) positive. (There is no absolute convention of colouring, and red/positive, blue/negative are often confusingly reversed!) Opaque isosurfaces do not allow the atoms to be seen and identified and it is not easy to deduce them. Because of this, isosurfaces are often drawn with a degree of transparency.

Technology

Molecular graphics has always pushed the limits of display technology, and has seen a number of cycles of integration and separation of compute-host and display. Early systems like Project MAC were bespoke and unique, but in the 1970s the MMS-X and similar systems used (relatively) low-cost terminals, such as the Tektronix 4014 series, often over dial-up lines to multi-user hosts. The devices could only display static pictures but, were able to evangelize MG. In the late 1970s, it was possible for departments (such as crystallography) to afford their own hosts (e.g., PDP-11) and to attach a display (such as Evans & Sutherland's MPS) directly to the bus. The display list was kept on the host, and interactivity was good since updates were rapidly reflected in the display—at the cost of reducing most machines to a single-user system.

In the early 1980s, Evans & Sutherland (E&S) decoupled their PS300 display, which contained its own display information transformable through a dataflow architecture. Complex graphical objects could be downloaded over a serial line (e.g. 9600 baud) and then manipulated without impact on the host. The architecture was excellent for high performance display but very inconvenient for domain-specific calculations, such as electron-density fitting and energy calculations. Many crystallographers and modellers spent arduous months trying to fit such activities into this architecture.

The benefits for MG were considerable, but by the later 1980s, UNIX workstations such as Sun-3 with raster graphics (initially at a resolution of 256 by 256) had started to appear. Computer-assisted drug design in particular required raster graphics for the display of computed properties such as atomic charge and electrostatic potential. Although E&S had a high-end range of raster graphics (primarily aimed at the aerospace industry) they failed to respond to the low-end market challenge where single users, rather than engineering departments, bought workstations. As a result the market for MG displays passed to Silicon Graphics, coupled with the development of minisupercomputers (e.g., CONVEX and Alliant) which were affordable for well-supported MG laboratories. Silicon Graphics provided a graphics language, IrisGL, which was easier to use and more productive than the PS300 architecture. Commercial companies (e.g., Biosym, Polygen/MSI) ported their code to Silicon Graphics, and by the early 1990s, this was the "industry standard".

Stereoscopic displays were developed based on liquid crystal polarized spectacles, and while this had been very expensive on the PS300, it now became a commodity item. A common alternative was to add a polarizable screen to the front of the display and to provide viewers with extremely cheap spectacles with orthogonal polarization for separate eyes. With projectors such as Barco, it was possible to project stereoscopic display onto special silvered screens and supply an audience of hundreds with spectacles. In this way molecular graphics became universally known within large sectors of chemical and biochemical science, especially in the pharmaceutical industry. Because the backgrounds of many displays were black by default, it was common for modelling sessions and lectures to be held with almost all lighting turned off.

In the last decade almost all of this technology has become commoditized. IrisGL evolved to OpenGL so that molecular graphics can be run on any machine. In 1992, Roger Sayle released his RasMol program into the public domain. RasMol contained a very high-performance molecular renderer that ran on Unix/X Window, and Sayle later ported this to the Windows and Macintosh platforms. The Richardsons developed kinemages and the Mage software, which was also multi-platform. By specifying the chemical MIME type,

molecular models could be served over the Internet, so that for the first time MG could be distributed at zero cost regardless of platform. In 1995, Birkbeck College's crystallography department used this to run "Principles of Protein Structure", the first multimedia course on the Internet, which reached 100 to 200 scientists.

Fig. 6. A molecule of Porin (protein) shown without ambient occlusion (left) and with (right). Advanced rendering effects can improve the comprehension of the 3D shape of a molecule.
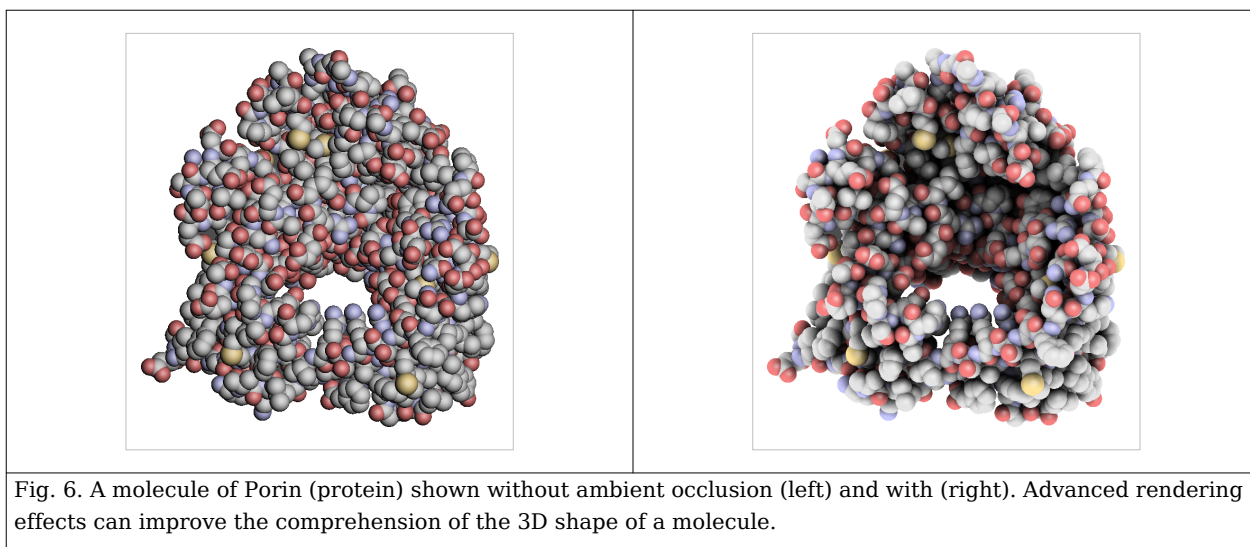
MG continues to see innovation that balances technology and art, and currently zero-cost or open source programs such as PyMOL and Jmol have very wide use and acceptance.

Recently the wide spread diffusion of advanced graphics hardware, has improved the rendering capabilities of the visualization tools. The capabilities of current shading languages allow the inclusion of advanced graphic effects (like ambient occlusion, cast shadows and non-photorealistic rendering techniques) in the interactive visualization of molecules. These graphic effects, beside being eye candy, can improve the comprehension of the three dimensional shapes of the molecules. An example of the effects that can be achieved exploiting recent graphics hardware can be seen in the simple open source visualization system QuteMol.

Algorithms

Reference frames

Drawing molecules requires a transformation between molecular coordinates (usually, but not always, in Angstrom units) and the screen. Because many molecules are chiral it is essential that the handedness of the system (almost always right-handed) is preserved. In molecular graphics the origin (0, 0) is usually at the lower left, while in many computer systems the origin is at top left. If the z-coordinate is out of the screen (towards the viewer) the molecule will be referred to right-handed axes, while the screen display will be left-handed.

Molecular transformations normally require:

• scaling of the display (but not the molecule).
• translations of the molecule and objects on the screen.
• rotations about points and lines.

Conformational changes (e.g. rotations about bonds) require rotation of one part of the molecule relative to another. The programmer must decide whether a transformation on the

screen reflects a change of view or a change in the molecule or its reference frame.

Simple
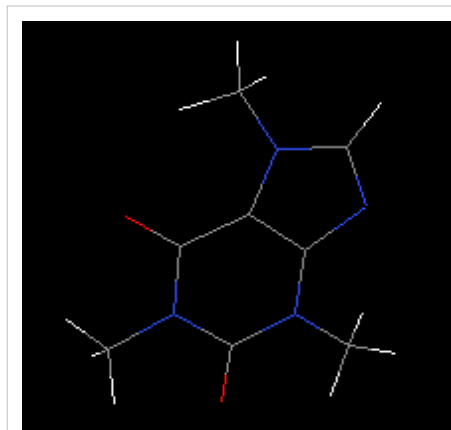
Fig. 7. Stick model of caffeine drawn in Jmol.

In early displays only vectors could be drawn e.g. (Fig. 7) which are easy to draw because no rendering or hidden surface removal is required.

On vector machines the lines would be smooth but on raster devices Bresenham's algorithm is used (note the "jaggies" on some of the bonds, which can be largely removed with antialiasing software.)

Atoms can be drawn as circles, but these should be sorted so that those with the largest z-coordinates (nearest the screen) are drawn last. Although imperfect, this often gives a reasonably attractive display. Other simple tricks which do not include hidden surface algorithms are:

- colouring each end of a bond with the same colour as the atom to which it is attached (Fig. 7).
- drawing less than the whole length of the bond (e.g. 10%-90%) to simulate the bond sticking out of a circle.
- adding a small offset white circle within the circle for an atom to simulate reflection.

Typical pseudocode for creating Fig. 7 (to fit the molecule exactly to the screen):

```
// assume:
// atoms with x, y, z coordinates (Angstrom) and elementSymbol
// bonds with pointers/references to atoms at ends
// table of colours for elementTypes
// find limits of molecule in molecule coordinates as xMin, yMin, xMax,
 yMax
scale = min(xScreenMax/(xMax-xMin), yScreenMax/(yMax-yMin))
xOffset = -xMin * scale; yOffset = -yMin * scale
for (bond in $bonds) {
  atom0 = bond.getAtom(0)
  atom1 = bond.getAtom(1)
  x0 = xOffset+atom0.getX()*scale; y0 = yOffset+atom0.getY()*scale //
(1)
  x1 = xOffset+atom1.getX()*scale; y1 = yOffset+atom1.getY()*scale //
(2)
  x1 = atom1.getX();  y1 = atom1.getY()
  xMid = (x0 + x1) /2;  yMid = (y0 + y1) /2;
  colour0 = ColourTable.getColour(atom0.getSymbol())
  drawLine (colour0, x0, y0, xMid, yMid)
  colour1 = ColourTable.getColour(atom1.getSymbol())
  drawLine (colour1, x1, y1, xMid, yMid)
}
```

Note that this assumes the origin is in the bottom left corner of the screen, with Y up the screen. Many graphics systems have the origin at the top left, with Y down the screen. In this case the lines (1) and (2) should have the y coordinate generation as:

```
y0 = yScreenMax -(yOffset+atom0.getY()*scale) // (1)
y1 = yScreenMax -(yOffset+atom1.getY()*scale) // (2)
```

Changes of this sort change the handedness of the axes so it is easy to reverse the chirality of the displayed molecule unless care is taken.

Advanced

For greater realism and better comprehension of the 3D structure of a molecule many computer graphics algorithms can be used. For many years molecular graphics has stressed the capabilities of graphics hardware and has required hardware-specific approaches. With the increasing power of machines on the desktop, portability is more important and programs such as Jmol have advanced algorithms that do not rely on hardware. On the other hand recent graphics hardware is able to interactively render very complex molecule shapes with a quality that would not be possible with standard software techniques.

Chronology

This table provides an incomplete chronology of molecular graphics advances.

Developer(s)	Approximate date	Technology	Comments
Crystallographers	< 1960	Hand-drawn	Crystal structures, with hidden atom and bond removal. Often clinographic projections.
Cyrus Levinthal, Bob Langridge	1960s	CRT	First protein display on screen (Project MAC).
Johnson, Motherwell	ca 1970	Pen plotter	ORTEP, PLUTO. Very widely deployed for publishing crystal structures.
Langridge, White, Marshall	Late 1970s	Departmental systems (PDP-11, Tektronix displays or DEC-VT11, e.g. MMS-X)	Mixture of commodity computing with early displays.
T. Alwyn Jones	1978	FRODO	Crystallographic structure solution.
Davies, Hubbard	Mid-1980s	CHEM-X, HYDRA	Laboratory systems with multicolor, raster and vector devices (Sigmex, PS300).
Biosym, Tripos, Polygen	Mid-1980s	PS300 and lower cost dumb terminals (VT200, SIGMEX)	Commercial integrated modelling and display packages.
Silicon Graphics, Sun	Late 1980s	IRIS GL (UNIX) workstations	Commodity-priced single-user workstations with stereoscopic display.
EMBL - WHAT IF [4]	1989, 2000	Machine independent	Nearly free, multifunctional, still fully supported, many free servers [5] based on it

Sayle, Richardson	1992, 1993	RasMol, Kinemage	Platform-independent MG.
MDL (van Vliet, Maffett, Adler, Holt)	1995-1998	Chime	proprietary C++ ; free browser plugin for Mac (OS9) and PCs
ChemAxon	1998-	MarvinSketch [6] & MarvinView [7] . MarvinSpace [8] (2005)	proprietary Java applet or stand-alone application.
Community efforts	2000-	Jmol, PyMol, Protein Workshop (www.pdb.org)	Open-source Java applet or stand-alone application.
NOCH	2002-	NOC [9]	Powerful and open source code molecular structure explorer
LION Bioscience / EMBL	2004-	SRS 3D [10]	Free, open-source system based on Java3D. Integrates 3D structures with sequence and feature data (domains, SNPs, etc.).
San Diego Supercomputer Center	2006-	Sirius	Free for academic/non-profit institutions
Weizmann Institute of Science - Community efforts	2008-	Proteopedia	Collaborative, 3D wiki encyclopedia of proteins & other molecules

References

[1] Dickerson, R.E.; Geis, I. (1969). *The structure and action of proteins*. Menlo Park, CA: W.A. Benjamin.
[2] International Union of Pure and Applied Chemistry (1997). " molecular graphics (http://goldbook.iupac.org/ MT06970.html)". *Compendium of Chemical Terminology* Internet edition.
[3] http://www.scripps.edu/mb/goodsell/mgs_art/
[4] http://swift.cmbi.ru.nl/whatif/
[5] http://swift.cmbi.ru.nl/
[6] http://www.chemaxon.com/product/msketch.html
[7] http://www.chemaxon.com/product/mview.html
[8] http://www.chemaxon.com/product/mspace.html
[9] http://noch.sourceforge.net
[10] http://srs3d.org

See also

- List of Molecular Graphics Systems
- Molecular Design software
- Molecular model
- Molecular modelling
- Molecular geometry
- Software for molecular mechanics modeling

External links

- The PyMOL Molecular Graphics System (http://pymol.sf.net) -- open source
  - PyMOLWiki (http://pymolwiki.org) -- community supported wiki for PyMOL
- History of Visualization of Biological Macromolecules (http://www.umass.edu/microbio/rasmol/history.htm) by Eric Martz and Eric Francoeur.
- Brief History of Molecular Mechanics/Graphics (http://stanley.chem.lsu.edu/webpub/7770-Lecture-1-intro.pdf) in LSU CHEM7770 lecture notes.
- Historical slides (http://luminary.stanford.edu/langridge/slides.htm) from Robert (Bob) Langridge. These show the influence of Crick and Watson on molecular graphics (including Levinthal's) and the development of early display technology, finishing with displays which were common in the mid-1980s on machines such as Evans and Sutherland's PS300 series.
- Interview with Langridge. (http://luminary.stanford.edu/langridge/langridge.html) The display looking down the axis of B-DNA has been likened to a rose window.
- Nelson Max's home page (http://accad.osu.edu/~waynec/history/tree/max.html) with links to 1982 classics.
- Jmol home page (http://jmol.sourceforge.net/) contains an applet with an automatic display of many features of molecular graphics including metaphors, scripting, annotation and animation.
- Richardson Lab (http://kinemage.biochem.duke.edu/) includes Kinemage and molecular graphics images.
- History of RasMol. (http://www.openrasmol.org/history.html)
- Molecule of the Month (http://www.rcsb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/index.html) at RCSB/PDB.
- xeo (http://sourceforge.net/projects/xeo) xeo is a free (GPL) open project management for nanostructures using Java
- Exhibitions of Molecular Graphics Art (http://www.scripps.edu/mb/goodsell/mgs_art/), 1994, 1998.
- NOCH home page (http://noch.sourceforge.net) A powerful, efficient and open source molecular graphics tool.
- eMovie (http://www.weizmann.ac.il/ISPC/eMovie.html): a tool for creation of molecular animations with PyMOL.
- Proteopedia (http://www.proteopedia.org): The collaborative, 3D encyclopedia of proteins and other molecules.
- Ascalaph Graphics (http://www.agilemolecule.com/Ascalaph/Ascalaph_Graphics.html): a molecular viewer with some geometry editing capabilities.
- Molecular Graphics and Modelling Society. (http://www.mgms.org/)
- *Journal of Molecular Graphics and Modelling* (http://www.sciencedirect.com/science?_ob=JournalURL&_cdi=5260&_auth=y&_acct=C000053194&_version=1&_urlVersion=0&_userid=1495569&md5=1e86bcce088e98890cea52f6eda84b64) (formally *Journal of Molecular Graphics*). This journal is not open access.

Mathematical, Logical and Theoretical Physics Foundations

Theoretical physics

Theoretical physics employs mathematical models and abstractions of physics in an attempt to explain natural phenomena in a mathematical form. Its central core is mathematical physics [1], though other conceptual techniques are also used. The goal is to rationalize, explain and predict physical phenomena. The advancement of science depends in general on the interplay between experimental studies and theory. In some cases, theoretical physics adheres to standards of mathematical rigor while giving little weight to experiments and observations. For example, while developing special relativity, Albert Einstein was concerned with the Lorentz transformation which left Maxwell's equations invariant, but was apparently uninterested in the Michelson-Morley experiment on Earth's drift through a luminiferous ether. On the other hand, Einstein was awarded the Nobel Prize for explaining the photoelectric effect, previously an experimental result lacking a theoretical formulation.

Overview

A **physical theory** is a model of physical events. It is judged by the extent to which its predictions agree with empirical observations. The quality of a physical theory is also judged on its ability to make new predictions which can be verified by new observations. A physical theory differs from a mathematical theorem in that while both are based on some form of axioms, judgment of mathematical applicability is not based on agreement with any experimental results.

> $$\mathrm{Ricci} = k\, g$$
>
> *The equations for an Einstein manifold, used in general relativity to describe the curvature of spacetime*

A physical theory involves one or more relationships between various measurable quantities. Archimedes realized that a ship floats by displacing its mass of water, Pythagoras understood the relation between the length of a vibrating string and the musical tone it produces, and how to calculate the length of a rectangle's diagonal. Other examples include entropy as a measure of the uncertainty regarding the positions and motions of unseen particles and the quantum mechanical idea that (action and) energy are not continuously variable.

Sometimes the vision provided by pure mathematical systems can provide clues to how a physical system might be modeled; e.g., the notion, due to Riemann and others, that space itself might be curved.

Theoretical advances may consist in setting aside old, incorrect paradigms (e.g., Burning consists of evolving phlogiston, or Astronomical bodies revolve around the Earth) or may be an alternative model that provides answers that are more accurate or that can be more

widely applied.

Physical theories become accepted if they are able to make correct predictions and (few) incorrect ones. The theory should have, at least as a secondary objective, a certain economy and elegance (compare to mathematical beauty), a notion sometimes called "Occam's razor" after the 13th-century English philosopher William of Occam (or Ockham), in which the simpler of two theories that describe the same matter just as adequately is preferred. (But conceptual simplicity may mean mathematical complexity.) They are also more likely to be accepted if they connect a wide range of phenomena. Testing the consequences of a theory is part of the scientific method.

Physical theories can be grouped into three categories: *mainstream theories*, *proposed theories* and *fringe theories*.

History

Theoretical physics began at least 2,300 years ago, under the pre-Socratic Greek philosophers, and continued by Plato; and Aristotle, whose views held sway for a millennium. In medieval times, during the rise of the universities, the only acknowledged intellectual disciplines were theology, mathematics, medicine, and law. As the concepts of matter, energy, space, time and causality slowly began to acquire the form we know today, other sciences spun off from the rubric of natural philosophy. During the Middle Ages and Renaissance, the concept of experimental science, the counterpoint to theory, began with scholars such as Ibn al-Haytham and Francis Bacon. The modern era of theory began perhaps with the Copernican paradigm shift in astronomy, soon followed by Johannes Kepler's expressions for planetary orbits, which summarized the meticulous observations of Tycho Brahe.

The great push toward the modern concept of explanation started with Galileo, one of the few physicists who was both a consummate theoretician and a great experimentalist. The analytic geometry and mechanics of Descartes were incorporated into the calculus and mechanics of Isaac Newton, another theoretician/experimentalist of the highest order. Joseph-Louis Lagrange, Leonhard Euler and William Rowan Hamilton would extend the theory of classical mechanics considerably. Each of these individuals picked up the interactive intertwining of mathematics and physics begun two millennia earlier by Pythagoras.

Among the great conceptual achievements of the 19th and 20th centuries were the consolidation of the idea of energy by the inclusion of heat, then electricity and magnetism and light, and finally mass. The laws of thermodynamics, and especially the introduction of the singular concept of entropy began to provide a macroscopic explanation for the properties of matter.

The pillars of modern physics, and perhaps the most revolutionary theories in the history of physics, have been relativity theory and quantum mechanics. Newtonian mechanics was subsumed under special relativity and Newton's gravity was given a kinematic explanation by general relativity. Quantum mechanics led to an understanding of blackbody radiation and of anomalies in the specific heats of solids — and finally to an understanding of the internal structures of atoms and molecules.

All of these achievements depended on the theoretical physics as a moving force both to suggest experiments and to consolidate results — often by ingenious application of existing mathematics, or, as in the case of Descartes and Newton (with Leibniz), by inventing new

mathematics. Fourier's studies of heat conduction led to a new branch of mathematics: infinite, orthogonal series.

Modern theoretical physics attempts to unify theories and explain phenomena in further attempts to understand the Universe, from the cosmological to the elementary particle scale. Where experimentation cannot be done, theoretical physics still tries to advance through the use of mathematical models. Some of their most prominent and well thought out advancements in this field include:

Prominent theoretical physicists

Famous *theoretical physicists* include

- Christiaan Huyghens (1629-1695)
- Isaac Newton (1643-1727)
- Leonhard Euler (1707-1783)
- Joseph Louis Lagrange (1736-1813)
- Pierre-Simon Laplace (1749-1827)
- Joseph Fourier (1768-1830)
- Nicolas Léonard Sadi Carnot (1796-1842)
- William Rowan Hamilton (1805-1865)
- Rudolf Clausius (1822-1888)
- James Clerk Maxwell (1831-1879)
- J. Willard Gibbs (1839-1903)
- Ludwig Boltzmann (1844-1906)
- Hendrik A. Lorentz (1853-1928)
- Henri Poincare (1854-1912)
- Nikola Tesla (1856-1943)
- Max Planck (1858-1947)
- Albert Einstein (1879-1955)
- Amalie Emmy Noether (1882-1935)
- Niels Bohr (1885-1962)
- Max Born (1882-1970)
- Erwin Schrödinger (1887-1961)
- Louis de Broglie (1892-1987)
- Satyendra Nath Bose (1894-1974)
- Wolfgang Pauli (1900-1958)
- Enrico Fermi (1901-1954)
- Werner Heisenberg (1901-1976)
- Paul Dirac (1902-1984)
- Eugene Wigner (1902-1995)
- Robert Oppenheimer (1904-1967)
- Sin-Itiro Tomonaga (1906-1979)
- Hideki Yukawa (1907-1981)
- Lev Landau (1908-1967)
- John Bardeen (1908-1991)
- Anatoly Vlasov (1908-1975)
- Nikolay Bogolyubov (1909-1992)
- Subrahmanyan Chandrasekhar (1910-1995)
- Julian Schwinger (1918-1994)

- Richard Feynman (1918-1988)
- Feza Gursey (1921-1992)
- Chen Ning Yang (1922-)
- Freeman Dyson (1923-)
- Gunnar Källén (1926-1968)
- Abdus Salam (1926-1996)
- Murray Gell-Mann (1929-)
- Riazuddin (1930-)
- George Sudarshan (1931-)
- Roger Penrose (1931-)
- Sheldon Glashow (1932-)
- Steven Weinberg (1933-)
- C. R. Hagen (1936 -)
- Michael Berry (1941-)
- Stephen Hawking (1942-)
- Alexander Polyakov (1945-)
- Gerardus 't Hooft (1946-)
- Jacob Bekenstein (1947-)
- Bertrand Halperin
- Robert Laughlin (1950-)
- Edward Witten (1951-)

Mainstream theories

Mainstream theories (sometimes referred to as *central theories*) are the body of knowledge of both factual and scientific views and possess a usual scientific quality of the tests of repeatability, consistency with existing well-established science and experimentation. There do exist mainstream theories that are generally accepted theories based solely upon their effects explaining a wide variety of data, although the detection, explanation and possible composition are subjects of debate.

Examples

- Black hole thermodynamics
- Classical mechanics
- Condensed matter physics
- Dynamics
- Dark matter
- Electromagnetism
- Field theory
- Fluid dynamics
- Solid mechanics
- General relativity
- Molecular modeling
- Particle physics
- Physical cosmology
- Quantum computers
- Quantum mechanics

- Quantum field theory
- Quantum information theory
- Quantum electrodynamics
- Quantum electrochemistry
- Quantum chromodynamics
- Solid state physics or Condensed Matter Physics and the electronic structure of materials
- Special relativity
- Standard Model
- Statistical mechanics
- Conservation of energy
- Thermodynamics

Proposed theories

The **proposed theories** of physics are usually relatively new theories which deal with the study of physics which include scientific approaches, means for determining the validity of models and new types of reasoning used to arrive at the theory. However, some proposed theories include theories that have been around for decades and have eluded methods of discovery and testing. Proposed theories can include fringe theories in the process of becoming established (and, sometimes, gaining wider acceptance). Proposed theories usually have not been tested.

Examples

- Causal Sets
- Dark energy or Einstein's Cosmological Constant
- Einstein-Rosen Bridge
- Emergence
- Grand unification theory
- Loop quantum gravity
- M-theory
- String theory
- Supersymmetry
- Theory of everything

Fringe theories

Fringe theories include any new area of scientific endeavor in the process of becoming established and some proposed theories. It can include speculative sciences. This includes physics fields and physical theories presented in accordance with known evidence, and a body of associated predictions have been made according to that theory.

Some fringe theories go on to become a widely accepted part of physics. Other fringe theories end up being disproven. Some fringe theories are a form of protoscience and others are a form of pseudoscience. The falsification of the original theory sometimes leads to reformulation of the theory.

Examples

- Dynamic theory of gravity
- Grand unification theory
- Luminiferous aether
- Steady state theory
- Theory of everything
- Metatheory

"Thought Experiments" versus real experiments

Important is also the subtle difference between "Thought Experiments" and real experiments. The "Thought Experiment" is theoretical, whereas real experiments belong to "Experimental Physics". A good example for this difference is the paper by *Albert Einstein and coworkers* on the EPR effect (1935), which (by the discovery of the consequences of the possibility of entanglement of quantum-mechanical states) confirms again Einstein's incredible logical sharpness and creativity, which led him to important conclusions (important till now, see e.g. quantum cryptography), although the paper contains philosophical assumptions on a certain *reality and locality* of physical properties which were basically wrong[1] , and could be falsified later-on by real experiments. In any case, the wrong basic assumptions led Einstein to the erroneous conclusion of a necessity to complement quantum theory, e.g. by "hidden variables". The falsification of the above-mentioned assumptions was by definite experiments, e.g. those of Alain Aspect, based on rigorous theoretical work of the Bell inequalities. Einstein's († 1955) work was also rigorous, apart from the underlying basic postulate that quantum mechanics should be of essentially "classical" nature, as e.g. Newton's mechanics or Maxwell's electrodynamics. Only after Bell's inequalities (1964) this assumption could be falsified by real experiments.

See also

- Experimental physics
- List of theoretical physicists

References

[1] See e.g. U. Krey, A. Owen, *Basic Theoretical Physics - A Concise Overview*, Berlin, Springer 2007

Notes

- Note 1: Sometimes *mathematical physics* and *theoretical physics* are used synonymously to refer to the latter.

External links

- Timeline of Theoretical Physics (http://superstringtheory.com/history/history3.html)
- MIT Center for Theoretical Physics (http://ctp.lns.mit.edu/index.html)
- Electronic Journal of Theoretical Physics (EJTP) (http://www.ejtp.com)
- How to Become a Theoretical Physicist by a Nobel Laureate (http://www.phys.uu.nl/~thooft/theorist.html)
- Theory of longitudinal and transversal angular momentums (http://www.odomann.com)

Dynamical system

The **dynamical system** concept is a mathematical formalization for any fixed "rule" which describes the time dependence of a point's position in its ambient space. Examples include the mathematical models that describe the swinging of a clock pendulum, the flow of water in a pipe, and the number of fish each spring in a lake.

At any given time a dynamical system has a *state* given by a set of real numbers (a vector) which can be represented by a point in an appropriate *state space* (a geometrical manifold). Small changes in the state of the system correspond to small changes in the numbers. The *evolution rule* of the dynamical system is a fixed rule that describes what future states follow from the current state. The rule is deterministic: for a given time interval only one future state follows from the current state.
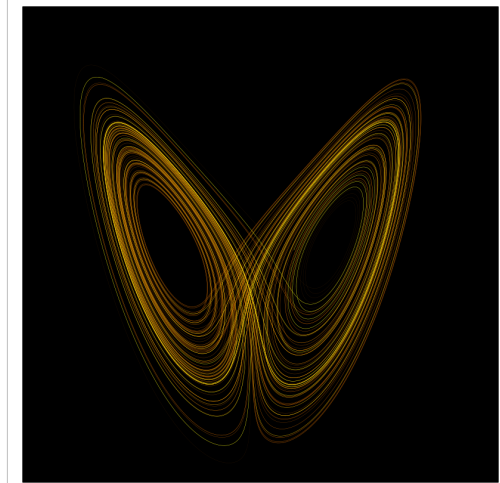
The Lorenz attractor is an example of a non-linear dynamical system. Studying this system helped give rise to Chaos theory.

Overview

The concept of a dynamical system has its origins in Newtonian mechanics. There, as in other natural sciences and engineering disciplines, the evolution rule of dynamical systems is given implicitly by a relation that gives the state of the system only a short time into the future. (The relation is either a differential equation, difference equation or other time scale.) To determine the state for all future times requires iterating the relation many times—each advancing time a small step. The iteration procedure is referred to as *solving the system* or *integrating the system*. Once the system can be solved, given an initial point it is possible to determine all its future points, a collection known as a *trajectory* or *orbit*.

Before the advent of fast computing machines, solving a dynamical system required sophisticated mathematical techniques and could only be accomplished for a small class of dynamical systems. Numerical methods executed on computers have simplified the task of determining the orbits of a dynamical system.

For simple dynamical systems, knowing the trajectory is often sufficient, but most dynamical systems are too complicated to be understood in terms of individual trajectories. The difficulties arise because:

- The systems studied may only be known approximately—the parameters of the system may not be known precisely or terms may be missing from the equations. The approximations used bring into question the validity or relevance of numerical solutions. To address these questions several notions of stability have been introduced in the study of dynamical systems, such as Lyapunov stability or structural stability. The stability of the dynamical system implies that there is a class of models or initial conditions for which the trajectories would be equivalent. The operation for comparing orbits to establish their equivalence changes with the different notions of stability.

- The type of trajectory may be more important than one particular trajectory. Some trajectories may be periodic, whereas others may wander through many different states of the system. Applications often require enumerating these classes or maintaining the system within one class. Classifying all possible trajectories has led to the qualitative study of dynamical systems, that is, properties that do not change under coordinate changes. Linear dynamical systems and systems that have two numbers describing a state are examples of dynamical systems where the possible classes of orbits are understood.
- The behavior of trajectories as a function of a parameter may be what is needed for an application. As a parameter is varied, the dynamical systems may have bifurcation points where the qualitative behavior of the dynamical system changes. For example, it may go from having only periodic motions to apparently erratic behavior, as in the transition to turbulence of a fluid.
- The trajectories of the system may appear erratic, as if random. In these cases it may be necessary to compute averages using one very long trajectory or many different trajectories. The averages are well defined for ergodic systems and a more detailed understanding has been worked out for hyperbolic systems. Understanding the probabilistic aspects of dynamical systems has helped establish the foundations of statistical mechanics and of chaos.

It was in the work of Poincaré that these dynamical systems themes developed.

Basic definitions

A dynamical system is a manifold M called the phase (or state) space and a smooth evolution function Φ^t that for any element of $t \ \square \ T$, the time, maps a point of the phase space back into the phase space. The notion of smoothness changes with applications and the type of manifold. There are several choices for the set T. When T is taken to be the reals, the dynamical system is called a *flow*; and if T is restricted to the non-negative reals, then the dynamical system is a *semi-flow*. When T is taken to be the integers, it is a *cascade* or a *map*; and the restriction to the non-negative integers is a *semi-cascade*.

Examples

The evolution function Φ^t is often the solution of a *differential equation of motion*

$$\dot{x} = v(x)\,.$$

The equation gives the time derivative, represented by the dot, of a trajectory $x(t)$ on the phase space starting at some point x_0. The *vector field* $v(x)$ is a smooth function that at every point of the phase space M provides the velocity vector of the dynamical system at that point. (These vectors are not vectors in the phase space M, but in the tangent space TM_x of the point x.) Given a smooth Φ^t, an autonomous vector field can be derived from it.

There is no need for higher order derivatives in the equation, nor for time dependence in $v(x)$ because these can be eliminated by considering systems of higher dimensions. Other types of differential equations can be used to define the evolution rule:

$$G(x, \dot{x}) = 0$$

is an example of an equation that arises from the modeling of mechanical systems with complicated constraints.

The differential equations determining the evolution function Φ^t are often ordinary differential equations: in this case the phase space M is a finite dimensional manifold. Many of the concepts in dynamical systems can be extended to infinite-dimensional manifolds—those that are locally Banach spaces—in which case the differential equations are partial differential equations. In the late 20th century the dynamical system perspective to partial differential equations started gaining popularity.

Further examples

- Logistic map
- Double pendulum
- Arnold's cat map
- Horseshoe map
- Baker's map is an example of a chaotic piecewise linear map
- Billiards and outer billiards
- Hénon map
- Lorenz system
- Circle map
- Rössler map
- List of chaotic maps
- Swinging Atwood's machine
- Quadratic map simulation system
- Bouncing ball simulation system

Linear dynamical systems

Linear dynamical systems can be solved in terms of simple functions and the behavior of all orbits classified. In a linear system the phase space is the N-dimensional Euclidean space, so any point in phase space can be represented by a vector with N numbers. The analysis of linear systems is possible because they satisfy a superposition principle: if *u(t)* and *w(t)* satisfy the differential equation for the vector field (but not necessarily the initial condition), then so will *u(t) + w(t)*.

Flows

For a flow, the vector field $\Phi(x)$ is a linear function of the position in the phase space, that is,

$$\phi(x) = Ax + b\,,$$

with *A* a matrix, *b* a vector of numbers and *x* the position vector. The solution to this system can be found by using the superposition principle (linearity). The case $b \neq 0$ with $A = 0$ is just a straight line in the direction of *b*:

$$\Phi^t(x_1) = x_1 + bt\,.$$

When *b* is zero and $A \neq 0$ the origin is an equilibrium (or singular) point of the flow, that is, if $x_0 = 0$, then the orbit remains there. For other initial conditions, the equation of motion is given by the exponential of a matrix: for an initial point x_0,

$$\Phi^t(x_0) = e^{tA}x_0\,.$$

When $b = 0$, the eigenvalues of *A* determine the structure of the phase space. From the eigenvalues and the eigenvectors of *A* it is possible to determine if an initial point will

converge or diverge to the equilibrium point at the origin.

The distance between two different initial conditions in the case $A \neq 0$ will change exponentially in most cases, either converging exponentially fast towards a point, or diverging exponentially fast. Linear systems display sensitive dependence on initial conditions in the case of divergence. For nonlinear systems this is one of the (necessary but not sufficient) conditions for chaotic behavior.

Linear vector fields and a few trajectories.
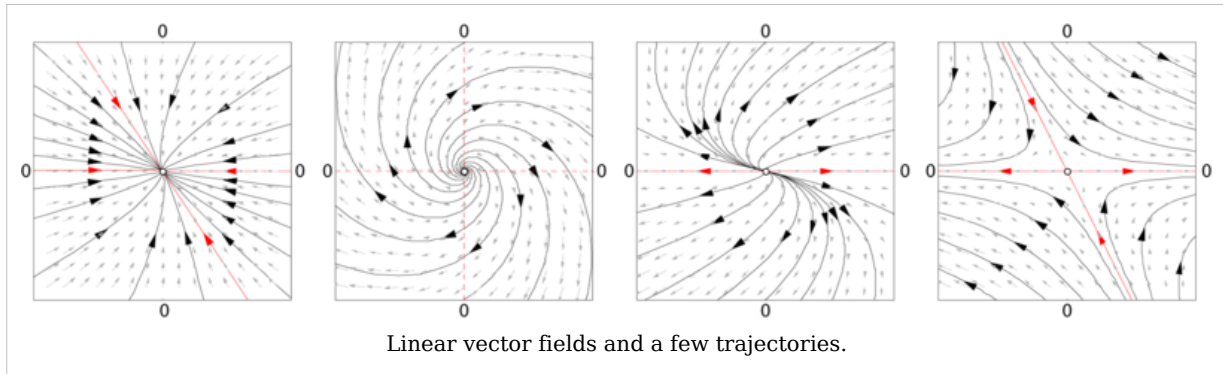
Maps

A discrete-time, affine dynamical system has the form

$$x_{n+1} = Ax_n + b,$$

with A a matrix and b a vector. As in the continuous case, the change of coordinates $x \to x + (1 - A)^{-1}b$ removes the term b from the equation. In the new coordinate system, the origin is a fixed point of the map and the solutions are of the linear system $A^n x_0$. The solutions for the map are no longer curves, but points that hop in the phase space. The orbits are organized in curves, or fibers, which are collections of points that map into themselves under the action of the map.

As in the continuous case, the eigenvalues and eigenvectors of A determine the structure of phase space. For example, if u_1 is an eigenvector of A, with a real eigenvalue smaller than one, then the straight lines given by the points along $\alpha\, u_1$, with $\alpha \in \mathbf{R}$, is an invariant curve of the map. Points in this straight line run into the fixed point.

There are also many other discrete dynamical systems.

Local dynamics

The qualitative properties of dynamical systems do not change under a smooth change of coordinates (this is sometimes taken as a definition of qualitative): a *singular point* of the vector field (a point where $v(x) = 0$) will remain a singular point under smooth transformations; a *periodic orbit* is a loop in phase space and smooth deformations of the phase space cannot alter it being a loop. It is in the neighborhood of singular points and periodic orbits that the structure of a phase space of a dynamical system can be well understood. In the qualitative study of dynamical systems, the approach is to show that there is a change of coordinates (usually unspecified, but computable) that makes the dynamical system as simple as possible.

Rectification

A flow in most small patches of the phase space can be made very simple. If y is a point where the vector field $v(y) \neq 0$, then there is a change of coordinates for a region around y where the vector field becomes a series of parallel vectors of the same magnitude. This is known as the rectification theorem.

The rectification theorem says that away from singular points the dynamics of a point in a small patch is a straight line. The patch can sometimes be enlarged by stitching several patches together, and when this works out in the whole phase space M the dynamical system is *integrable*. In most cases the patch cannot be extended to the entire phase space. There may be singular points in the vector field (where $v(x) = 0$); or the patches may become smaller and smaller as some point is approached. The more subtle reason is a global constraint, where the trajectory starts out in a patch, and after visiting a series of other patches comes back to the original one. If the next time the orbit loops around phase space in a different way, then it is impossible to rectify the vector field in the whole series of patches.

Near periodic orbits

In general, in the neighborhood of a periodic orbit the rectification theorem cannot be used. Poincaré developed an approach that transforms the analysis near a periodic orbit to the analysis of a map. Pick a point x_0 in the orbit γ and consider the points in phase space in that neighborhood that are perpendicular to $v(x_0)$. These points are a Poincaré section $S(\gamma, x_0)$, of the orbit. The flow now defines a map, the Poincaré map $F : S \rightarrow S$, for points starting in S and returning to S. Not all these points will take the same amount of time to come back, but the times will be close to the time it takes x_0.

The intersection of the periodic orbit with the Poincaré section is a fixed point of the Poincaré map F. By a translation, the point can be assumed to be at $x = 0$. The Taylor series of the map is $F(x) = J \cdot x + O(x^2)$, so a change of coordinates h can only be expected to simplify F to its linear part

$$h^{-1} \circ F \circ h(x) = J \cdot x \,.$$

This is known as the conjugation equation. Finding conditions for this equation to hold has been one of the major tasks of research in dynamical systems. Poincaré first approached it assuming all functions to be analytic and in the process discovered the non-resonant condition. If $\lambda_1,...,\lambda_\nu$ are the eigenvalues of J they will be resonant if one eigenvalue is an integer linear combination of two or more of the others. As terms of the form $\lambda_i - \sum$ (multiples of other eigenvalues) occurs in the denominator of the terms for the function h, the non-resonant condition is also known as the small divisor problem.

Conjugation results

The results on the existence of a solution to the conjugation equation depend on the eigenvalues of J and the degree of smoothness required from h. As J does not need to have any special symmetries, its eigenvalues will typically be complex numbers. When the eigenvalues of J are not in the unit circle, the dynamics near the fixed point x_0 of F is called *hyperbolic* and when the eigenvalues are on the unit circle and complex, the dynamics is called *elliptic*.

In the hyperbolic case the Hartman-Grobman theorem gives the conditions for the existence of a continuous function that maps the neighborhood of the fixed point of the map to the linear map $J \cdot x$. The hyperbolic case is also *structurally stable*. Small changes in the vector field will only produce small changes in the Poincaré map and these small changes will reflect in small changes in the position of the eigenvalues of J in the complex plane, implying that the map is still hyperbolic.

The Kolmogorov-Arnold-Moser (KAM) theorem gives the behavior near an elliptic point.

Bifurcation theory

When the evolution map Φ^t (or the vector field it is derived from) depends on a parameter μ, the structure of the phase space will also depend on this parameter. Small changes may produce no qualitative changes in the phase space until a special value μ_0 is reached. At this point the phase space changes qualitatively and the dynamical system is said to have gone through a bifurcation.

Bifurcation theory considers a structure in phase space (typically a fixed point, a periodic orbit, or an invariant torus) and studies its behavior as a function of the parameter μ. At the bifurcation point the structure may change its stability, split into new structures, or merge with other structures. By using Taylor series approximations of the maps and an understanding of the differences that may be eliminated by a change of coordinates, it is possible to catalog the bifurcations of dynamical systems.

The bifurcations of a hyperbolic fixed point x_0 of a system family F_μ can be characterized by the eigenvalues of the first derivative of the system $DF_\mu(x_0)$ computed at the bifurcation point. For a map, the bifurcation will occur when there are eigenvalues of DF_μ on the unit circle. For a flow, it will occur when there are eigenvalues on the imaginary axis. For more information, see the main article on Bifurcation theory.

Some bifurcations can lead to very complicated structures in phase space. For example, the Ruelle-Takens scenario describes how a periodic orbit bifurcates into a torus and the torus into a strange attractor. In another example, Feigenbaum period-doubling describes how a stable periodic orbit goes through a series of period-doubling bifurcations.

Ergodic systems

In many dynamical systems it is possible to choose the coordinates of the system so that the volume (really a ν-dimensional volume) in phase space is invariant. This happens for mechanical systems derived from Newton's laws as long as the coordinates are the position and the momentum and the volume is measured in units of (position) × (momentum). The flow takes points of a subset A into the points $\Phi^t(A)$ and invariance of the phase space means that

$$\mathrm{vol}(A) = \mathrm{vol}(\Phi^t(A)) \,.$$

In the Hamiltonian formalism, given a coordinate it is possible to derive the appropriate (generalized) momentum such that the associated volume is preserved by the flow. The volume is said to be computed by the Liouville measure.

In a Hamiltonian system not all possible configurations of position and momentum can be reached from an initial condition. Because of energy conservation, only the states with the same energy as the initial condition are accessible. The states with the same energy form an energy shell Ω, a sub-manifold of the phase space. The volume of the energy shell,

computed using the Liouville measure, is preserved under evolution.

For systems where the volume is preserved by the flow, Poincaré discovered the recurrence theorem: Assume the phase space has a finite Liouville volume and let F be a phase space volume-preserving map and A a subset of the phase space. Then almost every point of A returns to A infinitely often. The Poincaré recurrence theorem was used by Zermelo to object to Boltzmann's derivation of the increase in entropy in a dynamical system of colliding atoms.

One of the questions raised by Boltzmann's work was the possible equality between time averages and space averages, what he called the ergodic hypothesis. The hypothesis states that the length of time a typical trajectory spends in a region A is vol(A)/vol(Ω).

The ergodic hypothesis turned out not to be the essential property needed for the development of statistical mechanics and a series of other ergodic-like properties were introduced to capture the relevant aspects of physical systems. Koopman approached the study of ergodic systems by the use of functional analysis. An observable a is a function that to each point of the phase space associates a number (say instantaneous pressure, or average height). The value of an observable can be computed at another time by using the evolution function φ^t. This introduces an operator U^t, the transfer operator,

$$(U^t a)(x) = a(\Phi^{-t}(x)).$$

By studying the spectral properties of the linear operator U it becomes possible to classify the ergodic properties of Φ^t. In using the Koopman approach of considering the action of the flow on an observable function, the finite-dimensional nonlinear problem involving Φ^t gets mapped into an infinite-dimensional linear problem involving U.

The Liouville measure restricted to the energy surface Ω is the basis for the averages computed in equilibrium statistical mechanics. An average in time along a trajectory is equivalent to an average in space computed with the Boltzmann factor $\exp(-\beta H)$. This idea has been generalized by Sinai, Bowen, and Ruelle (SRB) to a larger class of dynamical systems that includes dissipative systems. SRB measures replace the Boltzmann factor and they are defined on attractors of chaotic systems.

Chaos theory

Simple nonlinear dynamical systems and even piecewise linear systems can exhibit a completely unpredictable behavior, which might seem to be random. (Remember that we are speaking of completely deterministic systems!). This seemingly unpredictable behavior has been called *chaos*. Hyperbolic systems are precisely defined dynamical systems that exhibit the properties ascribed to chaotic systems. In hyperbolic systems the tangent space perpendicular to a trajectory can be well separated into two parts: one with the points that converge towards the orbit (the *stable manifold*) and another of the points that diverge from the orbit (the *unstable manifold*).

This branch of mathematics deals with the long-term qualitative behavior of dynamical systems. Here, the focus is not on finding precise solutions to the equations defining the dynamical system (which is often hopeless), but rather to answer questions like "Will the system settle down to a steady state in the long term, and if so, what are the possible attractors?" or "Does the long-term behavior of the system depend on its initial condition?"

Note that the chaotic behavior of complicated systems is not the issue. Meteorology has been known for years to involve complicated—even chaotic—behavior. Chaos theory has

been so surprising because chaos can be found within almost trivial systems. The logistic map is only a second-degree polynomial; the horseshoe map is piecewise linear.

Geometrical definition

A dynamical system is the tuple $\langle \mathcal{M}, f, \mathcal{T} \rangle$, with $\mathcal{M}$ a manifold (locally a Banach space or Euclidean space), $\mathcal{T}$ the domain for time (non-negative reals, the integers, ...) and f an evolution rule t→f^t (with $t \in \mathcal{T}$) such that f^t is a diffeomorphism of the manifold to itself. So, f is a mapping of the time-domain $\mathcal{T}$ into the space of diffeomorphisms of the manifold to itself. In other terms, f(t) is a diffeomorphism, for every time t in the domain $\mathcal{T}$.

Measure theoretical definition

See main article measure-preserving dynamical system.

A dynamical system may be defined formally, as a measure-preserving transformation of a sigma-algebra, the quadruplet (X, Σ, μ, τ). Here, *X* is a set, and Σ is a sigma-algebra on *X*, so that the pair (X, Σ) is a measurable space. μ is a finite measure on the sigma-algebra, so that the triplet (X, Σ, μ) is a probability space. A map $\tau : X \to X$ is said to be Σ-measurable if and only if, for every $\sigma \in \Sigma$, one has $\tau^{-1}\sigma \in \Sigma$. A map τ is said to **preserve the measure** if and only if, for every $\sigma \in \Sigma$, one has $\mu(\tau^{-1}\sigma) = \mu(\sigma)$. Combining the above, a map τ is said to be a **measure-preserving transformation of X**, if it is a map from *X* to itself, it is Σ-measurable, and is measure-preserving. The quadruple (X, Σ, μ, τ), for such a τ, is then defined to be a **dynamical system**.

The map τ embodies the time evolution of the dynamical system. Thus, for discrete dynamical systems the iterates $\tau^n = \tau \circ \tau \circ \ldots \circ \tau$ for integer *n* are studied. For continuous dynamical systems, the map τ is understood to be finite time evolution map and the construction is more complicated.

Examples of dynamical systems

Wikipedia links

- Arnold's cat map
- Baker's map is an example of a chaotic piecewise linear map
- Circle map
- Double pendulum
- Billiards and Outer Billiards
- Henon map
- Horseshoe map
- Irrational rotation
- List of chaotic maps
- Logistic map
- Lorenz system
- Rossler map

External links

- Bouncing Ball [1]
- Mechanical Strings [2]
- Journal of Advanced Research in Dynamical and Control Systems [3]
- Swinging Atwood's Machine (SAM) [4]
- Interactive applet for the Standard and Henon Maps [5] by A. Luhn

See also

- Behavioral modeling
- Dynamical systems theory
- List of dynamical system topics
- Oscillation
- People in systems and control
- Sarkovskii's theorem
- System dynamics
- Systems theory

References

[1] http://www.drchaos.net/drchaos/bb.html
[2] http://www.drchaos.net/drchaos/string_web_page/index.html
[3] http://www.i-asr.org/dynamic.html
[4] http://www.drchaos.net/drchaos/Sam/sam.html
[5] http://complexity.xozzox.de/nonlinmappings.html

Further reading

Works providing a broad coverage:

- Ralph Abraham and Jerrold E. Marsden (1978). *Foundations of mechanics*. Benjamin-Cummings. ISBN 0-8053-0102-X. (available as a reprint: ISBN 0-201-40840-6)
- *Encyclopaedia of Mathematical Sciences* (ISSN 0938-0396) has a sub-series on dynamical systems (http://en.wikipedia.org/wiki/User:XaosBits/EMP) with reviews of current research.
- Anatole Katok and Boris Hasselblatt (1996). *Introduction to the modern theory of dynamical systems*. Cambridge. ISBN 0-521-57557-5.
- Christian Bonatti, Lorenzo J. Díaz, Marcelo Viana (2005). *Dynamics Beyond Uniform Hyperbolicity: A Global Geometric and Probabilistic Perspective*. Springer. ISBN 3-540-22066-6.
- Diederich Hinrichsen and Anthony J. Pritchard (2005). *Mathematical Systems Theory I - Modelling, State Space Analysis, Stability and Robustness*. Springer Verlag. ISBN 978-3-540-44125-0.

Introductory texts with a unique perspective:

- V. I. Arnold (1982). *Mathematical methods of classical mechanics*. Springer-Verlag. ISBN 0-387-96890-3.
- Jacob Palis and Wellington de Melo (1982). *Geometric theory of dynamical systems: an introduction*. Springer-Verlag. ISBN 0-387-90668-1.

- David Ruelle (1989). *Elements of Differentiable Dynamics and Bifurcation Theory*. Academic Press. ISBN 0-12-601710-7.
- Tim Bedford, Michael Keane and Caroline Series, *eds.* (1991). *Ergodic theory, symbolic dynamics and hyperbolic spaces*. Oxford University Press. ISBN 0-19-853390-X.
- Ralph H. Abraham and Christopher D. Shaw (1992). *Dynamics—the geometry of behavior, 2nd edition*. Addison-Wesley. ISBN 0-201-56716-4.

Textbooks

- Steven H. Strogatz (1994). *Nonlinear dynamics and chaos: with applications to physics, biology chemistry and engineering*. Addison Wesley. ISBN 0-201-54344-3.
- Kathleen T. Alligood, Tim D. Sauer and James A. Yorke (2000). *Chaos. An introduction to dynamical systems*. Springer Verlag. ISBN 0-387-94677-2.
- Morris W. Hirsch, Stephen Smale and Robert Devaney (2003). *Differential Equations, dynamical systems, and an introduction to chaos*. Academic Press. ISBN 0-12-349703-5.

Popularizations:

- Florin Diacu and Philip Holmes (1996). *Celestial Encounters*. Princeton. ISBN 0-691-02743-9.
- James Gleick (1988). *Chaos: Making a New Science*. Penguin. ISBN 0-14-009250-1.
- Ivar Ekeland (1990). *Mathematics and the Unexpected (Paperback)*. University Of Chicago Press. ISBN 0-226-19990-8.
- Ian Stewart (1997). *Does God Play Dice? The New Mathematics of Chaos*. Penguin. ISBN 0140256024.

External links

- A collection of dynamic and non-linear system models and demo applets (http://vlab. infotech.monash.edu.au/simulations/non-linear/) (in Monash University's Virtual Lab)
- Arxiv preprint server (http://www.arxiv.org/list/math.DS/recent) has daily submissions of (non-refereed) manuscripts in dynamical systems.
- DSWeb (http://www.dynamicalsystems.org/) provides up-to-date information on dynamical systems and its applications.
- Encyclopedia of dynamical systems (http://www.scholarpedia.org/article/ Encyclopedia_of_Dynamical_Systems) A part of Scholarpedia — peer reviewed and written by invited experts.
- Nonlinear Dynamics (http://www.egwald.ca/nonlineardynamics/index.php). Models of bifurcation and chaos by Elmer G. Wiens
- Oliver Knill (http://www.dynamical-systems.org) has a series of examples of dynamical systems with explanations and interactive controls.
- Sci.Nonlinear FAQ 2.0 (Sept 2003) (http://amath.colorado.edu/faculty/jdm/ faq-Contents.html) provides definitions, explanations and resources related to nonlinear science

Online books or lecture notes:

- Geometrical theory of dynamical systems (http://arxiv.org/pdf/math.HO/0111177). Nils Berglund's lecture notes for a course at ETH at the advanced undergraduate level.
- Dynamical systems (http://www.ams.org/online_bks/coll9/). George D. Birkhoff's 1927 book already takes a modern approach to dynamical systems.
- Chaos: classical and quantum (http://chaosbook.org). An introduction to dynamical systems from the periodic orbit point of view.

- Modeling Dynamic Systems (http://www.embedded.com/2000/0008/0008feat2.htm). An introduction to the development of mathematical models of dynamic systems.
- Learning Dynamical Systems (http://www.cs.brown.edu/research/ai/dynamics/tutorial/home.html). Tutorial on learning dynamical systems.
- Ordinary Differential Equations and Dynamical Systems (http://www.mat.univie.ac.at/~gerald/ftp/book-ode/). Lecture notes by Gerald Teschl

Research groups:

- Dynamical Systems Group Groningen (http://www.math.rug.nl/~broer/), IWI, University of Groningen.
- Chaos @ UMD (http://www-chaos.umd.edu/). Concentrates on the applications of dynamical systems.
- Dynamical Systems (http://www.math.sunysb.edu/dynamics/), SUNY Stony Brook. Lists of conferences, researchers, and some open problems.
- Center for Dynamics and Geometry (http://www.math.psu.edu/dynsys/), Penn State.
- Control and Dynamical Systems (http://www.cds.caltech.edu/), Caltech.
- Laboratory of Nonlinear Systems (http://lanoswww.epfl.ch/), Ecole Polytechnique Fédérale de Lausanne (EPFL).
- Center for Dynamical Systems (http://www.math.uni-bremen.de/ids.html/), University of Bremen
- Systems Analysis, Modelling and Prediction Group (http://www.eng.ox.ac.uk/samp/), University of Oxford
- Non-Linear Dynamics Group (http://sd.ist.utl.pt/), Instituto Superior Técnico, Technical University of Lisbon
- Dynamical Systems (http://www.impa.br/), IMPA, Instituto Nacional de Matemática Pura e Aplicada.
- Nonlinear Dynamics Workgroup (http://ndw.cs.cas.cz/), Institute of Computer Science, Czech Academy of Sciences.

Simulation software based on Dynamical Systems approach:

- FyDiK (http://fydik.kitnarf.cz/)

Bifurcation diagram

In mathematics, particularly in dynamical systems, a **bifurcation diagram** shows the possible long-term values (equilibria/fixed points or periodic orbits) of a system as a function of a bifurcation parameter in the system. It is usual to represent stable solutions with a solid line and unstable solutions with a dotted line.

Bifurcations in the 1D discrete dynamical systems (maps)

Logistic map

An example is the bifurcation diagram of the logistic map:

Bifurcation diagram of the logistic map
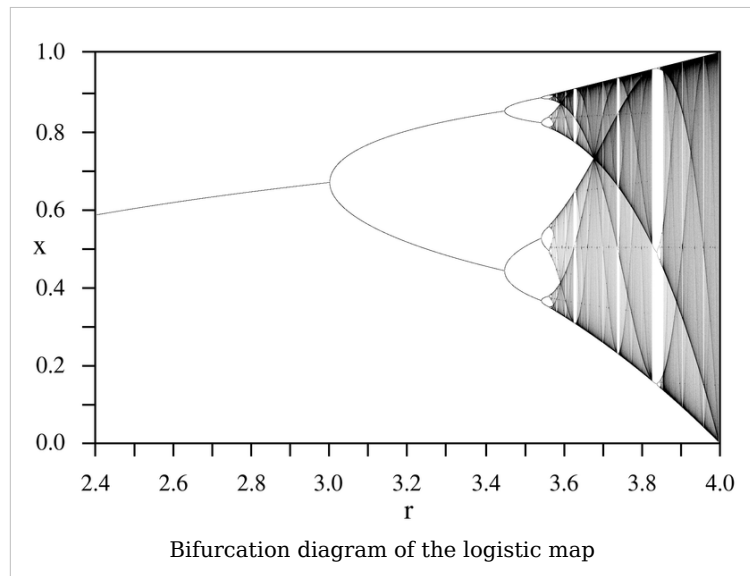
$$x_{n+1} = r x_n (1 - x_n).$$

The bifurcation parameter r is shown on the horizontal axis of the plot and the vertical axis shows the possible long-term population values of the logistic function. Only the stable solutions are shown here, there are many other unstable solutions which are not shown in this diagram.

The bifurcation diagram nicely shows the forking of the possible periods of stable orbits from 1 to 2 to 4 to 8 etc. Each of these bifurcation points is a period-doubling bifurcation. The ratio of the lengths of successive intervals between values of r for which bifurcation occurs converges to the first Feigenbaum constant.

Real quadratic map

For $x_{n+1} = x_n^2 - c$; the code in MATLAB can be written as:

```
close all;
clear all;
c=0;
y=0.0;

hold on
while c < 4
```

```
        for i=1:100;
            y = y.^2 -c; %converge the iteration
        end
        for i=1:20

            y = y.^2 - c;
            plot(c,y,'.'); % plot the converged points
        end
        c=c+0.01;
end
```

Symmetry breaking in bifurcation sets

In a dynamical system such as

Symmetry breaking in pitchfork bifurcation as the parameter epsilon is varied. epsilon = 0 is the case of symmetric pitchfork bifurcation.
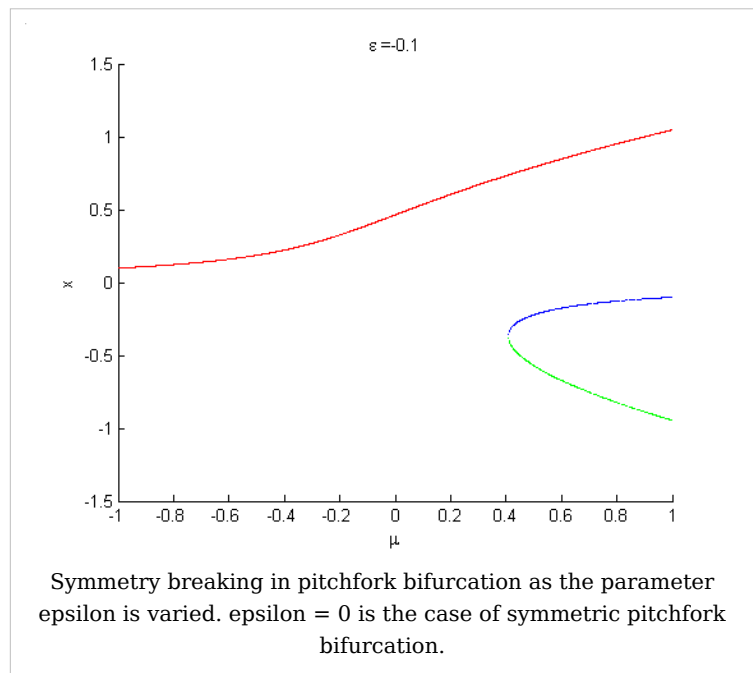
$$\ddot{x} + f(x;\mu) + \epsilon g(x) = 0,$$

which is structurally stable when $\mu \neq 0$, if a bifurcation diagram is plotted, treating μ as the bifurcation parameter, but for different values of ϵ, the case $\epsilon = 0$ is the symmetric pitchfork bifurcation. When $\epsilon \neq 0$, we say we have a pitchfork with *broken symmetry*. This is illustrated in the animation on the right.

See also

- Bifurcation theory
- Phase portrait

References

- Paul Glendinning, "Stability, Instability and Chaos", Cambridge University Press, 1994.
- Steven Strogatz, "Non-linear Dynamics and Chaos: With applications to Physics, Biology, Chemistry and Engineering", Perseus Books, 2000.

External links

- Logistic Map Simulation [1]. A Java applet simulating the Logistic Map by Yuval Baror.
- The Logistic Map and Chaos [2]
- A small application for drawing the Logistic Map [3]

References

[1] http://yuval.bar-or.org/index.php?item=4
[2] http://www.egwald.com/nonlineardynamics/logisticsmapchaos.php
[3] http://home.scarlet.be/kpm/vb/winattract.html

Phase space

In mathematics and physics, a **phase space**, introduced by Willard Gibbs in 1901, is a space in which all possible states of a system are represented, with each possible state of the system corresponding to one unique point in the phase space. For mechanical systems, the phase space usually consists of all possible values of position and momentum variables. A plot of position and momentum variables as a function of time is sometimes called a phase plot or a phase diagram. Phase diagram, however, is more usually reserved in the

Phase space of a dynamical system with focal stability.

physical sciences for a diagram showing the various regions of stability of the thermodynamic phases of a chemical system, which consists of pressure, temperature, and composition.
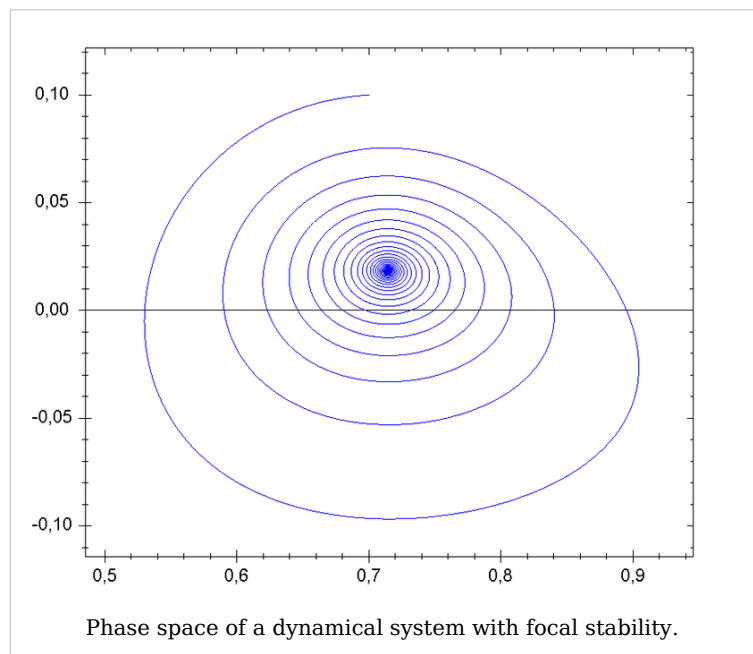
In a phase space, every degree of freedom or parameter of the system is represented as an axis of a multidimensional space. For every possible state of the system, or allowed combination of values of the system's parameters, a point is plotted in the multidimensional

space. Often this succession of plotted points is analogous to the system's state evolving over time. In the end, the phase diagram represents all that the system can be, and its shape can easily elucidate qualities of the system that might not be obvious otherwise. A phase space may contain very many dimensions. For instance, a gas containing many molecules may require a separate dimension for each particle's *x*, *y* and *z* positions and velocities as well as any number of other properties.

In classical mechanics the phase space co-ordinates are the generalized coordinates q_i and their conjugate generalized momenta p_i. The motion of an ensemble of systems in this space is studied by classical statistical mechanics. The local density of points in such systems obeys Liouville's Theorem, and so can be taken as constant. Within the context of a model system in classical mechanics, the phase space coordinates of the system at any given time are composed of all of the system's dynamical variables. Because of this, it is possible to calculate the state of the system at any given time in the future or the past, through integration of Hamilton's or Lagrange's equations of motion. Furthermore, because each point in phase space lies on exactly one phase trajectory, no two phase trajectories can intersect.

For simple systems, such as a single particle moving in one dimension for example, there may be as few as two degrees of freedom, (typically, position and velocity), and a sketch of the phase portrait may give qualitative information about the dynamics of the system, such as the limit-cycle of the Van der Pol oscillator shown in the diagram.

Here, the horizontal axis gives the position and vertical axis the velocity. As the system evolves, its state follows one of the lines (trajectories) on the phase diagram.

Classic examples of phase diagrams from chaos theory are the Lorenz attractor and Mandelbrot set.

Phase portrait of the Van der Pol oscillator

Quantum mechanics

In quantum mechanics, the coordinates *p* and *q* of phase space become hermitian operators in a Hilbert space, but may alternatively retain their classical interpretation, provided functions of them compose in novel algebraic ways (through Groenewold's 1946 star product). Every quantum mechanical observable corresponds to a unique function or distribution on phase space, and vice versa, as specified by Hermann Weyl (1927) and supplemented by John von Neumann (1931); Eugene Wigner (1932); and, in a grand synthesis, by H J Groenewold (1946). With José Enrique Moyal (1949), these completed the foundations of phase-space quantization, a logically autonomous reformulation of quantum mechanics. Its modern abstractions include deformation quantization and geometric quantization.
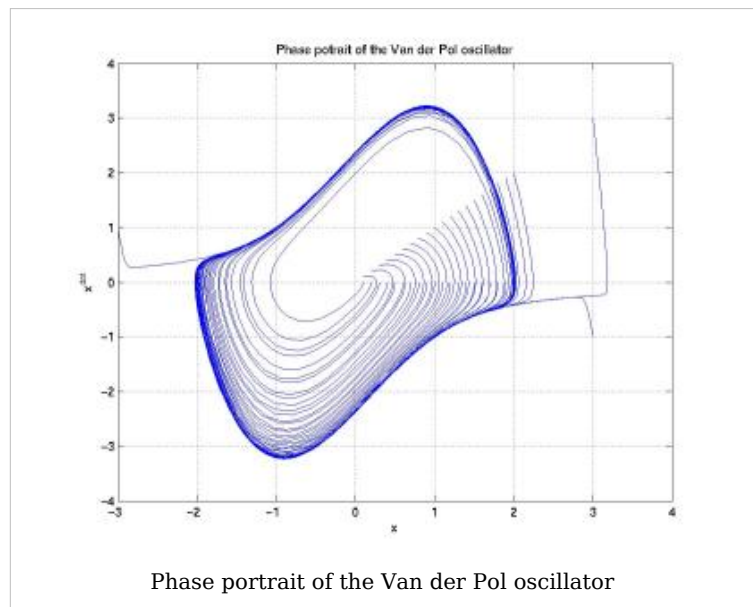
Thermodynamics and statistical mechanics

In thermodynamics and statistical mechanics contexts, the term phase space has two meanings: It is used in the same sense as in classical mechanics. If a thermodynamical system consists of N particles, then a point in the *6N*-dimensional phase space describes the dynamical state of every particle in that system, as each particle is associated with three position variables and three momentum variables. In this sense, a point in phase space is said to be a microstate of the system. N is typically on the order of Avogadro's number, thus describing the system at a microscopic level is often impractical. This leads us to the use of phase space in a different sense.

The phase space can refer to the space that is parametrized by the *macroscopic* states of the system, such as pressure, temperature, etc. For instance, one can view the pressure-volume diagram or entropy-temperature diagrams as describing part of this phase space. A point in this phase space is correspondingly called a macrostate. There may easily be more than one microstate with the same macrostate. For example, for a fixed temperature, the system could have many dynamic configurations at the microscopic level. When used in this sense, a phase is a region of phase space where the system in question is in, for example, the liquid phase, or solid phase, etc.

Since there are many more microstates than macrostates, the phase space in the first sense is usually a manifold of much larger dimensions than the second sense. Clearly, many more parameters are required to register every detail of the system up to the molecular or atomic scale than to simply specify, say, the temperature or the pressure of the system.

See also

- Classical mechanics
- Dynamical system
- Molecular dynamics
- Hamiltonian mechanics
- Lagrangian mechanics
- Cotangent bundle
- Symplectic manifold
- Phase plane
- Phase space method
- Parameter space
- Optical Phase Space
- State space (controls) for information about state space (similar to phase state) in control engineering.
- State space (physics) for information about state space in physics
- State space for information about state space with discrete states in computer science.

Phase portrait

A **phase portrait** is a geometric representation of the trajectories of a dynamical system in the phase plane. Each set of initial conditions is representated by a different curve, or point.

Phase portraits are an invaluable tool in studying dynamical systems. They consist of a plot of typical trajectories in the state space. This reveals information such as whether an attractor, a repellor or limit cycle is present for the chosen parameter value. The concept of topological equivalence is important in classifying the behaviour of systems by specifying when two different phase portraits represent the same qualitative dynamic behavior.

A phase portrait graph of a dynamical system depicts the system's trajectories (with arrows) and stable steady states (with dots) and unstable steady states (with circles) in a state space. The axes are of state variables.

Examples

- Simple pendulum see picture (right).
- Simple Harmonic Oscillator where the phase portrait is made up of ellipses centred at the origin, which is a fixed point.
- Van der Pol oscillator see picture (right).
- Bifurcation diagram
- Mandelbrot set

Potential energy and phase portrait of a simple pendulum. Note that the x-axis, being angular, wraps onto itself after every 2π radians.

Phase portrait of van der Pol's equation,

$$\frac{d^2y}{dt^2} + \epsilon(y^2 - 1)\frac{dy}{dt} + y = 0, \quad \epsilon = 1$$
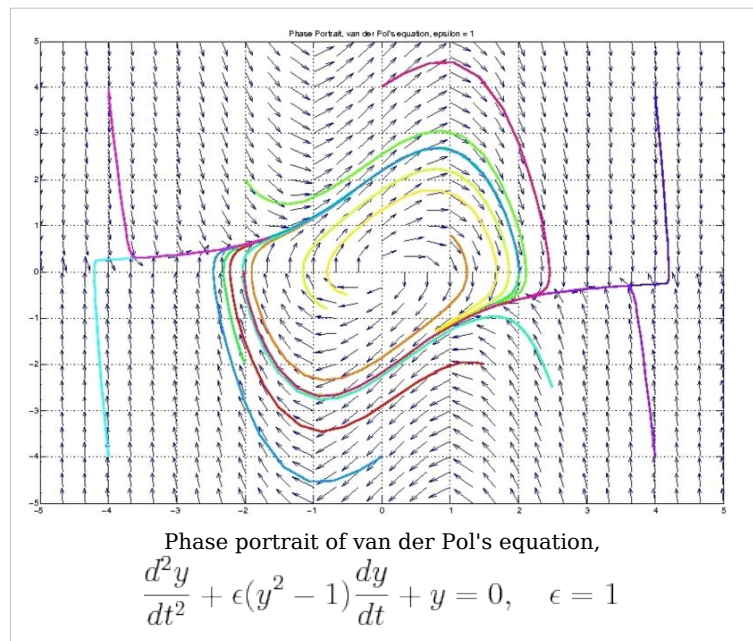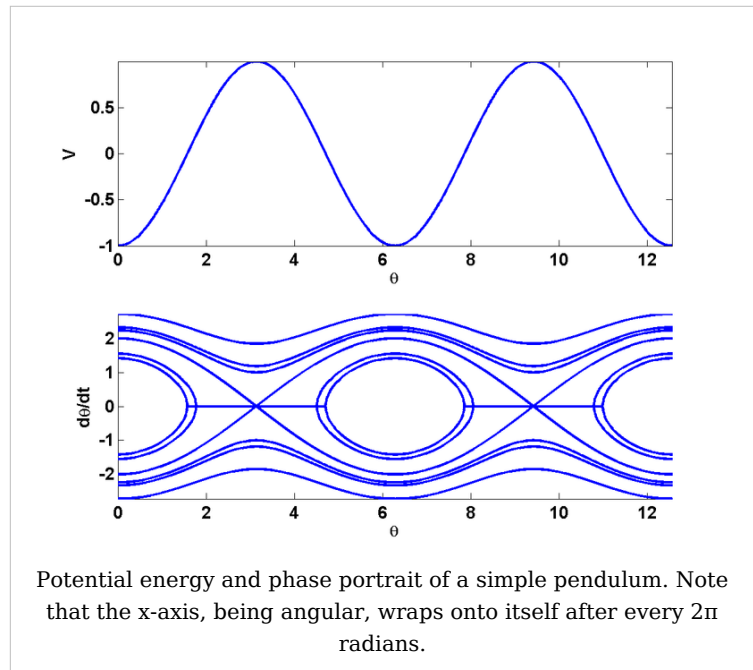
See also

- Phase space
- Phase plane
- Phase plane method

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Bifurcation theory

Bifurcation theory is the mathematical study of changes in the qualitative or topological structure of a given family. Examples of such families are the integral curves of a family of vector fields or, the solutions of a family of differential equations. Most commonly applied to the mathematical study of dynamical systems, a **bifurcation** occurs when a small smooth change made to the parameter values (the bifurcation parameters) of a system causes a sudden 'qualitative' or topological change in its behaviour. Bifurcations occur in both continuous systems (described by ODEs, DDEs or PDEs), and discrete systems (described by maps).

Bifurcation Types

It is useful to divide bifurcations into two principal classes:

- Local bifurcations, which can be analysed entirely through changes in the local stability properties of equilibria, periodic orbits or other invariant sets as parameters cross through critical thresholds; and
- Global bifurcations, which often occur when larger invariant sets of the system 'collide' with each other, or with equilibria of the system. They cannot be detected purely by a stability analysis of the equilibria (fixed points).

Local bifurcations

A local bifurcation occurs when a parameter change causes the stability of an equilibrium (or fixed point) to change. In continuous systems, this corresponds to the real part of an eigenvalue of an equilibrium passing through zero. In discrete systems (those described by maps rather than ODEs), this corresponds to a fixed point having a Floquet multiplier with modulus equal to one. In both cases, the equilibrium is *non-hyperbolic* at the bifurcation point. The topological changes in the phase portrait of the system can be confined to arbitrarily small neighbourhoods of the bifurcating fixed points by moving the bifurcation parameter close to the bifurcation point (hence 'local').

Phase portrait showing Saddle-node bifurcation.

Period-halving bifurcations (L) leading to order, followed by period doubling bifurcations (R) leading to chaos.

More technically, consider the continuous dynamical system described by the ODE
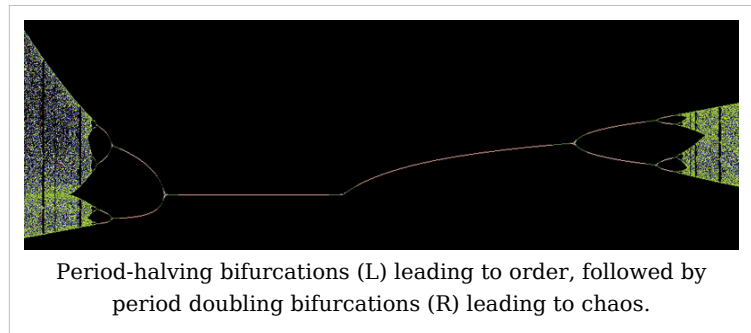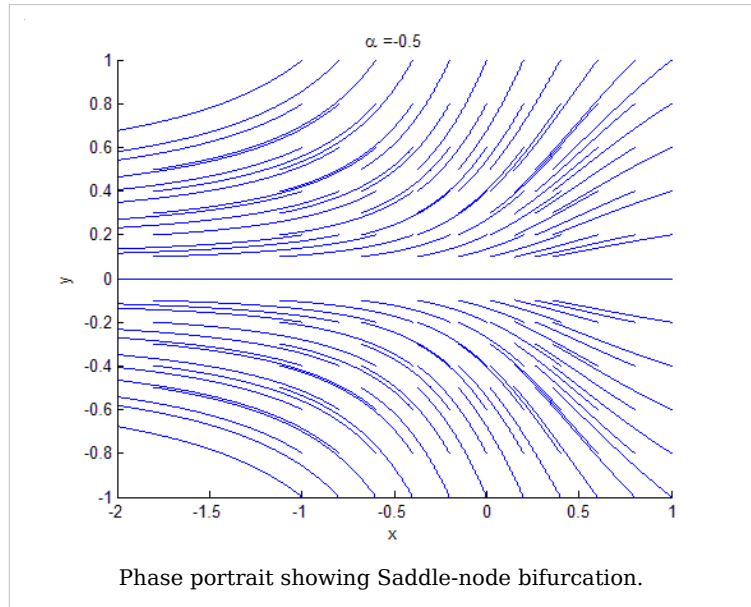
$$\dot{x} = f(x, \lambda) \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n.$$

A local bifurcation occurs at (x_0, λ_0) if the Jacobian matrix $\mathrm{d}f_{x_0,\lambda_0}$ has an eigenvalue with zero real part. If the eigenvalue is equal to zero, the bifurcation is a steady state bifurcation, but if the eigenvalue is non-zero but purely imaginary, this is a Hopf bifurcation.

For discrete dynamical systems, consider the system

$$x_{n+1} = f(x_n, \lambda).$$

Then a local bifurcation occurs at (x_0, λ_0) if the matrix $\mathrm{d}f_{x_0,\lambda_0}$ has an eigenvalue with modulus equal to one. If the eigenvalue is equal to one, the bifurcation is either a saddle-node (often called fold bifurcation in maps), transcritical or pitchfork bifurcation. If the eigenvalue is equal to -1, it is a period-doubling (or flip) bifurcation, and otherwise, it is a Hopf bifurcation.

Examples of local bifurcations include:

- Saddle-node (fold) bifurcation
- Transcritical bifurcation
- Pitchfork bifurcation
- Period-doubling (flip) bifurcation
- Hopf bifurcation

- Neimark (secondary Hopf) bifurcation

Global bifurcations

Global bifurcations occur when 'larger' invariant sets, such as periodic orbits, collide with equilibria. This causes changes in the topology of the trajectories in the phase space which cannot be confined to a small neighbourhood, as is the case with local bifurcations. In fact, the changes in topology extend out to an arbitrarily large distance (hence 'global').

Examples of global bifurcations include:

- Homoclinic bifurcation in which a limit cycle collides with a saddle point.
- Heteroclinic bifurcation in which a limit cycle collides with two or more saddle points.
- Infinite-period bifurcation in which a stable node and saddle point simultaneously occur on a limit cycle.
- Blue sky catastrophe in which a limit cycle collides with a nonhyperbolic cycle.

Global bifurcations can also involve more complicated sets such as chaotic attractors.

Codimension of a bifurcation

The codimension of a bifurcation is the number of parameters which must be varied for the bifurcation to occur. This corresponds to the codimension of the parameter set for which the bifurcation occurs within the full space of parameters. Saddle-node bifurcations are the only generic local bifurcations which are really codimension-one (the others all having higher codimension). However, often transcritical and pitchfork bifurcations are also often thought of as codimension-one, because the normal forms can be written with only one parameter.

An example of a well-studied codimension-two bifurcation is the Bogdanov-Takens bifurcation.

See also

- Bifurcation diagram
- Catastrophe theory
- Feigenbaum constant
- Phase portrait

References

- Nonlinear dynamics [1]
- Bifurcations and Two Dimensional Flows [2] by Elmer G. Wiens
- Introduction to Bifurcation theory [3] by John David Crawford

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[2] http://www.egwald.ca/nonlineardynamics/bifurcations.php

[3] http://prola.aps.org/abstract/RMP/v63/i4/p991_1

Relation algebra

In mathematics and abstract algebra, a **relation algebra** is a residuated Boolean algebra equipped with an involution called "converse". The motivating example of a relation algebra is the algebra 2^{X^2} of all binary relations on a set X, with $R \bullet S$ interpreted as the usual composition of binary relations and the converse of R as the inverse relation. Relation algebra emerged in the 19th century work of Augustus De Morgan and Charles Peirce, which culminated in the algebraic logic of Ernst Schröder. The present-day purely equational form or relation algebra was developed by Alfred Tarski and his students, starting in the 1940s.

Definition

A **relation algebra** $(L, \wedge, \vee, \neg, 0, 1, \bullet, \mathbf{I}, \rhd, \lhd, \breve{\ })$ is an algebraic structure such that

(i) $(L, \wedge, \vee, \bullet, \mathbf{I}, \rhd, \lhd)$ is a residuated Boolean algebra, and

(ii) the unary operation $x^{\breve{\ }}$ satisfies $x^{\breve{\ }} \rhd \mathbf{I} = x = \mathbf{I} \lhd x^{\breve{\ }}$.

Since $x \rhd y$ can be defined in terms of composition and converse as $x^{\breve{\ }} \bullet y$, and dually $x \lhd y$ as $x \bullet y^{\breve{\ }}$, it is not necessary to include $\rhd$ or $\lhd$ in the signature, which can therefore be simplified to $(L, \wedge, \vee, \neg, 0, 1, \bullet, \mathbf{I}, \breve{\ })$, the more usual form of the signature for relation algebras. On the other hand $x^{\breve{\ }}$ is definable as either $x \rhd \mathbf{I}$ or $\mathbf{I} \lhd x$, in which case a relation algebra can have the same signature as a residuated Boolean algebra. With that definition the axioms become $(x \rhd \mathbf{I}) \rhd \mathbf{I} = x = \mathbf{I} \lhd (\mathbf{I} \lhd x)$. But this simply asserts that $\rhd \mathbf{I}$ and $\mathbf{I} \lhd$ are involutions. Jónsson and Tsinakis have shown that if either one is an involution then so is the other and they are then the same operation, namely converse. This leads to a particularly straightforward definition:

A relation algebra is a residuated Boolean algebra $(L, \wedge, \vee, \neg, 0, 1, \bullet, \mathbf{I}, \rhd, \lhd)$ such that $\mathbf{I} \lhd$ is an involution.

When $x \lhd y$ is viewed as a form of quotient of x by y, with $\mathbf{I}$ as the corresponding multiplicative unit, $x^{\breve{\ }} = \mathbf{I} \lhd x$ can be understood as the *reciprocal* of x by syntactic analogy with $1/x$, a term some authors use synonymously with converse.

Since residuated Boolean algebras are axiomatized with finitely many equations, so are relation algebras, which therefore form a finitely axiomatized variety called **RA**, the variety of relation algebras.

Axioms

The axioms **B1-B10** below are adapted from Givant (2006: 283), and were first set out by Tarski in 1948.[1] This axiomatization is predicated on a relation algebra being an algebraic structure over some Cartesian square L, having signature $\langle L, \lor, \bullet, ^-, \ ^\smile, \mathbf{I} \rangle$ of type $\langle 2, 2, 1, 1, 0 \rangle$.

L is a Boolean algebra under binary disjunction, $\lor$, and unary complementation $()^-$:

B1: $A \lor B = B \lor A$

B2: $A \lor (B \lor C) = (A \lor B) \lor C$

B3: $(A^- \lor B)^- \lor (A^- \lor B^-)^- = A$

This axiomatization of Boolean algebra is due to Huntington (1933).

L is a monoid under binary composition ($\bullet$) and nullary identity $\mathbf{I}$:

B4: $A \bullet (B \bullet C) = (A \bullet B) \bullet C$

B5: $A \bullet \mathbf{I} = A$

Unary converse $()^\smile$ is an involution with respect to composition:

B6: $A^{\smile\smile} = A$

B7: $(A \bullet B)^\smile = B^\smile \bullet A^\smile$

Converse and composition distribute over disjunction:

B8: $(A \lor B)^\smile = A^\smile \lor B^\smile$

B9: $(A \lor B) \bullet C = (A \bullet C) \lor (B \bullet C)$

B10 is Tarski's equational form of the fact, discovered by Augustus De Morgan, that $A \bullet B \leq C^- \leftrightarrow A^\smile \bullet C \leq B^- \leftrightarrow C \bullet B^\smile \leq A^-$.

B10: $(A^\smile \bullet (A \bullet B)^-) \lor B^- = B^-$

These axioms are ZFC theorems; for the purely Boolean **B1-B3**, this fact is trivial. After each of the following axioms is shown the number of the corresponding theorem in chpt. 3 of Suppes (1960), an exposition of ZFC: **B4** 27, **B5** 45, **B6** 14, **B7** 26, **B8** 16, **B9** 23.

Expressing properties of binary relations in RA

The following table shows how many of the usual properties of binary relations can be expressed as succinct inequalities or equalities using **RA** operations. Below, an inequality of the form $A \leq B$ is shorthand for a Boolean equation of the form $A \lor B = B$.

The most complete set of results of this nature is chpt. C of Carnap (1958), where the notation is rather distant from those of this entry. Chpt. 3.2 of Suppes (1960) contains fewer results, but they are presented as ZFC theorems, using a notation that more resembles that of this entry. Neither Carnap nor Suppes formulate their results using the **RA** of this entry, or in an equational manner.

R is	If and only if:
Surjective	$R^\smile \bullet R \leq \mathbf{I}$
Injective ($R^\smile$ surjective)	$R \bullet R^\smile \leq \mathbf{I}$
1-to-1	R is surjective and injective.
Total or Connected	$\mathbf{I} \leq R \lor R^\smile$

Functional	
Function	R is functional and total.
1-1 Function	$R\breve{\ }\bullet R = \mathbf{I}$ and $R\bullet R\breve{\ } = \mathbf{I}$. R is total, functional, and injective.
Reflexive	$\mathbf{I} \le R$
Irreflexive	$R \wedge \mathbf{I} = \mathbf{0}$. $(\mathbf{0} = \mathbf{I}\breve{\ })$
Transitive	$R \bullet R \le R$
Preorder	R is reflexive and transitive.
Antisymmetric	$R \wedge R\breve{\ } \le \mathbf{I}$
Partial order	R is an antisymmetric preorder.
Total order	R is a total partial order.
Strict partial order	R is transitive and irreflexive.
Strict total order	R is a total strict partial order.
Symmetric	$R = R\breve{\ }$
Equivalence	$R \bullet R\breve{\ } = R$. R is a symmetric preorder.
Asymmetric	$R \ne R\breve{\ }$
Dense	$R \wedge \mathbf{0} \le (R \wedge \mathbf{0}) \bullet (R \wedge \mathbf{0})$.

Expressive power

The metamathematics of **RA** are discussed at length in Tarski and Givant (1987), and more briefly in Givant (2006).

RA consists entirely of equations manipulated using nothing more than uniform replacement and the substitution of equals for equals. Both rules are wholly familiar from school mathematics and from abstract algebra generally. Hence **RA** proofs are carried out in a manner familiar to all mathematicians, unlike the case in mathematical logic generally.

RA can express any (and up to logical equivalence, exactly the) first-order logic (FOL) formulas containing no more than three variables. (A given variable can be quantified multiple times as long as the quantifiers do not nest more than 3 deep.) Surprisingly, this fragment of FOL suffices to express Peano arithmetic and almost all axiomatic set theories ever proposed. Hence **RA** is, in effect, a way of algebraizing nearly all mathematics, while dispensing with FOL and its connectives, quantifiers, turnstiles, and modus ponens. Because **RA** can express Peano arithmetic and set theory, Gödel's incompleteness theorems apply to it; **RA** is incomplete, incompletable, and undecidable. (N.B. The Boolean algebra fragment of **RA** is complete and decidable.)

The **representable relation algebras**, forming the class **RRA**, are those relation algebras isomorphic to some relation algebra comprised of binary relations on some set, and closed under the standard interpretations of the **RA** operations. It is easily shown, e.g. using the method of pseudoelementary classes, that **RRA** is a quasivariety, that is, axiomatizable by a universal Horn theory. In 1950, Roger Lyndon proved the existence of equations holding in **RRA** that did not hold in **RA**, that is, the variety generated by **RRA** is a proper subvariety of the variety **RA**. In 1955, Alfred Tarski showed that **RRA** is itself a variety, which however, as shown by Donald Monk in 1964, has no finite axiomatization, unlike **RA** which is finitely

axiomatized by definition. That not every relation algebra is representable is a fundamental way relation algebras differ from Boolean algebras, which are always representable as sets of subsets of some set closed under union, intersection, and complement.

Examples

1. Any Boolean algebra can be turned into a relation algebra by interpreting conjunction as composition (the monoid multiplication •), i.e. $x•y$ is defined as $x∧y$. This interpretation requires that converse interpret identity ($y̆ = y$), and that both residuals $y\backslash x$ and x/y interpret the conditional $y→x$ (i.e., $¬y∨x$).

2. The motivating example of a relation algebra depends on the definition of a binary relation R on a set X as any subset $R ⊆ X^2$. The power set 2^{X^2} consisting of all binary relations on X is a Boolean algebra. While 2^{X^2} can be made a relation algebra by taking $R•S = R∧S$ as for the preceding example, the standard interpretation of • is instead given by $x(R•S)z = ∃y.xRySz$. That is, the pair (x,z) belongs to the relation $R•S$ just when there exists $y ∈ X$ such that $(x,y) ∈ R$ and $(y,z) ∈ S$. This interpretation uniquely determines $R\backslash S$ to consist of all pairs (y,z) such that for all $x ∈ X$, if xRy then xSz. Dually S/R consists of all pairs (x,y) such that for all $z ∈ X$, if yRz then xSz. The translation $y̆ = ¬(y\backslash¬I)$ then establishes the converse $R^{˘}$ of R as consisting of all pairs (y,x) such that $(x,y) ∈ R$.

3. An important generalization of the previous example is the power set 2^E where $E ⊆ X^2$ is any equivalence relation on the set X. This is a generalization because X^2 is itself an equivalence relation, namely the complete relation consisting of all pairs. While 2^E is not a subalgebra of 2^{X^2} when $E ≠ X^2$ (since in that case it does not contain the relation X^2, the top element 1 being E instead of X^2), it is nevertheless made a relation algebra using the same definitions of the operations. Its importance resides in the definition of a *representable relation algebra* as any relation algebra isomorphic to a subalgebra of the relation algebra 2^E for some equivalence relation E on some set. Refer to the previous section for more on the relevant metamathematics.

4. If group sum or product interprets composition, group inverse interprets converse, group identity interprets **I**, and if R is a one to one correspondence, so that $R^{˘}•R = R•R^{˘} = I$,[2] then L is a group as well as a monoid. **B4**-**B7** become well-known theorems of group theory, so that relation algebra becomes a proper extension of group theory as well as of Boolean algebra, a fact indicative of its great expressive power.

Historical remarks

DeMorgan founded **RA** in 1860, but C. S. Peirce took it much further and became fascinated with its philosophical power. The work of DeMorgan and Peirce came to be known mainly in the extended and definitive form Ernst Schröder gave it in Vol. 3 of his *Vorlesungen* (1890-1905). *Principia Mathematica* drew strongly on Schröder's **RA**, but acknowledged him only as the inventor of the notation. In 1912, Alwin Korselt proved that a particular formula in which the quantifiers were nested 4 deep had no **RA** equivalent.[3] This fact led to a loss of interest in **RA** until Tarski (1941) began writing about it. His students have continued to develop **RA** down to the present day. Tarski returned to **RA** in the 1970s with the help of Steven Givant; this collaboration resulted in the monograph Tarski and Givant (1987), the definitive reference for this subject. For more on the history of **RA**, see Maddux (1991, 2006).

Software

- RelMICS / Relational Methods in Computer Science [4] maintained by Wolfram Kahl [5]
- Carsten Sinz: ARA / An Automatic Theorem Prover for Relation Algebras [6]

See also

- Algebraic logic
- Allegory (category theory)
- Binary relation
- Cartesian product
- Cartesian square
- Composition of relations
- Converse of a relation
- Relational calculus
- Relational algebra
- Relative product of relations
- Residuated Boolean algebra
- Spatial-temporal reasoning
- Theory of relations
- Triadic relation
- Cylindric algebras
- Extension in logic
- Involution
- Logic of relatives
- Relation
- Relation construction
- Relation reduction

Footnotes

[1] Alfred Tarski (1948) "Abstract: Representation Problems for Relation Algebras," *Bulletin of the AMS* 54: 80.
[2] Tarski, A. (1941), p. 87.
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[4] http://relmics.mcmaster.ca/html/index.html
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External links

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  - Relation algebras (http://math.chapman.edu/structuresold/files/Relation_algebras.pdf). In Mathematical structures. (http://math.chapman.edu/cgi-bin/structures) If there are problems with LaTeX, see an old HTML version here. (http://math.chapman.edu/cgi-bin/structures.pl?Relation_algebras)
  - " Foundations of Relations and Kleene Algebra. (http://math.chapman.edu/~jipsen/talks/RelMiCS2006/JipsenRAKAtutorial.pdf)"
  - " Computer Aided Investigations of Relation Algebras. (http://www1.chapman.edu/~jipsen/dissertation/)"
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Category theory

In mathematics, **category theory** deals in an abstract way with mathematical structures and relationships between them: it abstracts from *sets* and *functions* to *objects* linked in diagrams by *morphisms* or *arrows*.

One of the simplest examples of a category (which is a very important concept in topology) is that of groupoid, defined as a category whose arrows or morphisms are all invertible. Categories now appear in most branches of mathematics and also in some areas of theoretical computer science where they correspond to types and mathematical physics where they can be used to describe vector spaces. Category theory provides both with a unifying notion and terminology. Categories were first introduced by Samuel Eilenberg and Saunders Mac Lane in 1942–45, in connection with algebraic topology.

A category with objects X, Y, Z and morphisms *f*, *g*
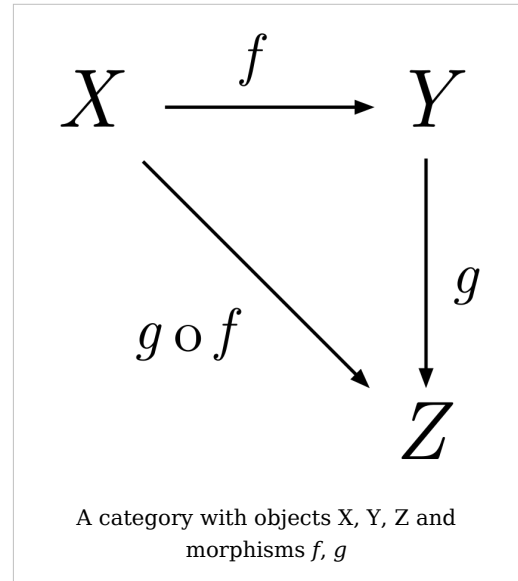
Category theory has several faces known not just to specialists, but to other mathematicians. A term dating from the 1940s, "general abstract nonsense", refers to its high level of abstraction, compared to more classical branches of mathematics. Homological algebra is category theory in its aspect of organising and suggesting manipulations in abstract algebra. Diagram chasing is a visual method of arguing with abstract "arrows" joined in diagrams. Note that arrows between categories are called functors, subject to specific defining commutativity conditions; moreover, categorical diagrams and sequences can be defined as functors (viz. Mitchell, 1965). An arrow between two functors is a natural transformation when it is subject to certain naturality or commutativity conditions. Both functors and natural transformations are key concepts in category theory, or the " real engines" of category theory. To paraphrase a famous sentence of the mathematicians who founded category theory: 'Categories were introduced to define functors, and functors were introduced to define natural transformations'. Topos theory is a form of abstract sheaf theory, with geometric origins, and leads to ideas such as pointless topology. A topos can also be considered as a specific type of category with two additional topos axioms.

Background

The study of categories is an attempt to *axiomatically* capture what is commonly found in various classes of related *mathematical structures* by relating them to the *structure-preserving functions* between them. A systematic study of category theory then allows us to prove general results about any of these types of mathematical structures from the axioms of a category.

Consider the following example. The class **Grp** of groups consists of all objects having a "group structure". More precisely, **Grp** consists of all sets G endowed with a binary operation satisfying a certain set of axioms. One can proceed to prove theorems about

groups by making logical deductions from the set of axioms. For example, it is immediately proved from the axioms that the identity element of a group is unique.

Instead of focusing merely on the individual objects (e.g., groups) possessing a given structure, category theory emphasizes the morphisms – the structure-preserving mappings – *between* these objects; it turns out that by studying these morphisms, we are able to learn more about the structure of the objects. In the case of groups, the morphisms are the group homomorphisms. A group homomorphism between two groups "preserves the group structure" in a precise sense – it is a "process" taking one group to another, in a way that carries along information about the structure of the first group into the second group. The study of group homomorphisms then provides a tool for studying general properties of groups and consequences of the group axioms.

A similar type of investigation occurs in many mathematical theories, such as the study of continuous maps (morphisms) between topological spaces in topology (the associated category is called **Top**), and the study of smooth functions (morphisms) in manifold theory.

If one axiomatizes relations instead of functions, one obtains the theory of allegories.

Functors

Abstracting again, a category is *itself* a type of mathematical structure, so we can look for "processes" which preserve this structure in some sense; such a process is called a functor. A functor associates to every object of one category an object of another category, and to every morphism in the first category a morphism in the second.

In fact, what we have done is define a category *of categories and functors* – the objects are categories, and the morphisms (between categories) are functors.

By studying categories and functors, we are not just studying a class of mathematical structures and the morphisms between them; we are studying the *relationships between various classes of mathematical structures*. This is a fundamental idea, which first surfaced in algebraic topology. Difficult *topological* questions can be translated into *algebraic* questions which are often easier to solve. Basic constructions, such as the fundamental group or fundamental groupoid [1] of a topological space, can be expressed as fundamental functors [1] to the category of groupoids in this way, and the concept is pervasive in algebra and its applications.

Natural transformation

Abstracting yet again, constructions are often "naturally related" – a vague notion, at first sight. This leads to the clarifying concept of natural transformation, a way to "map" one functor to another. Many important constructions in mathematics can be studied in this context. "Naturality" is a principle, like general covariance in physics, that cuts deeper than is initially apparent.

Historical notes

In 1942–45, Samuel Eilenberg and Saunders Mac Lane were the first to introduce categories, functors, and natural transformations as part of their work in topology, especially algebraic topology. Their work was an important part of the transition from intuitive and geometric homology to axiomatic homology theory. Eilenberg and Mac Lane later wrote that their goal was to understand natural transformations; in order to do that,

functors had to be defined, which required categories.

Stanislaw Ulam, and some writing on his behalf, have claimed that related ideas were current in the late 1930s in Poland. Eilenberg was Polish, and studied mathematics in Poland in the 1930s. Category theory is also, in some sense, a continuation of the work of Emmy Noether (one of Mac Lane's teachers) in formalizing abstract processes; Noether realized that in order to understand a type of mathematical structure, one needs to understand the processes preserving that structure. In order to achieve this understanding, Eilenberg and Mac Lane proposed an axiomatic formalization of the relation between structures and the processes preserving them.

The subsequent development of category theory was powered first by the computational needs of homological algebra, and later by the axiomatic needs of algebraic geometry, the field most resistant to being grounded in either axiomatic set theory or the Russell-Whitehead view of united foundations. General category theory, an extension of universal algebra having many new features allowing for semantic flexibility and higher-order logic, came later; it is now applied throughout mathematics.

Certain categories called topoi (singular *topos*) can even serve as an alternative to axiomatic set theory as a foundation of mathematics. These foundational applications of category theory have been worked out in fair detail as a basis for, and justification of, constructive mathematics. More recent efforts to introduce undergraduates to categories as a foundation for mathematics include Lawvere and Rosebrugh (2003) and Lawvere and Schanuel (1997).

Categorical logic is now a well-defined field based on type theory for intuitionistic logics, with applications in functional programming and domain theory, where a cartesian closed category is taken as a non-syntactic description of a lambda calculus. At the very least, category theoretic language clarifies what exactly these related areas have in common (in some abstract sense).

Categories, objects and morphisms

A *category C* consists of the following three mathematical entities:

- A class ob(*C*), whose elements are called *objects*;
- A class hom(*C*), whose elements are called morphisms or maps or *arrows*. Each morphism *f* has a unique *source object a* and *target object b*. We write *f*: *a* → *b*, and we say "*f* is a morphism from *a* to *b*". We write hom(*a*, *b*) (or Hom(*a*, *b*), or $\hom_C(a, b)$, or Mor(*a*, *b*), or *C*(*a*, *b*)) to denote the *hom-class* of all morphisms from *a* to *b*.
- A binary operation ∘, called *composition of morphisms*, such that for any three objects *a*, *b*, and *c*, we have hom(*a*, *b*) × hom(*b*, *c*) → hom(*a*, *c*). The composition of *f*: *a* → *b* and *g*: *b* → *c* is written as $g \circ f$ or *gf* (some authors write *fg*), governed by two axioms:

  - Associativity: If $f : a \to b$, $g : b \to c$ and $h : c \to d$ then $h \circ (g \circ f) = (h \circ g) \circ f$, and
  - Identity: For every object *x*, there exists a morphism $1_x : x \to x$ called the *identity morphism for x*, such that for every morphism $f : a \to b$, we have $1_b \circ f = f = f \circ 1_a$.

From these axioms, it can be proved that there is exactly one identity morphism for every object. Some authors deviate from the definition just given by identifying each object with its identity morphism.

Relations among morphisms (such as *fg* = *h*) are often depicted using commutative diagrams, with "points" (corners) representing objects and "arrows" representing

morphisms.

Properties of morphisms

Some morphisms have important properties. A morphism $f : a \rightarrow b$ is:

- a monomorphism (or *monic*) if $f{\circ}g_1 = f{\circ}g_2$ implies $g_1 = g_2$ for all morphisms $g_1, g_2 : x \rightarrow a$.
- an epimorphism (or *epic*) if $g_1{\circ}f = g_2{\circ}f$ implies $g_1 = g_2$ for all morphisms $g_1, g_2 : b \rightarrow x$.
- an isomorphism if there exists a morphism $g : b \rightarrow a$ with $f{\circ}g = 1_b$ and $g{\circ}f = 1_a$.[2]
- an endomorphism if $a = b$. end(a) denotes the class of endomorphisms of a.
- an automorphism if f is both an endomorphism and an isomorphism. aut(a) denotes the class of automorphisms of a.

Functors

Functors are structure-preserving maps between categories. They can be thought of as morphisms in the category of all (small) categories.

A (**covariant**) functor F from a category C to a category D, written $F{:}C \rightarrow D$, consists of:

- for each object x in C, an object $F(x)$ in D; and
- for each morphism $f : x \rightarrow y$ in C, a morphism $F(f) : F(x) \rightarrow F(y)$,

such that the following two properties hold:

- For every object x in C, $F(1_x) = 1_{F(x)}$;

- For all morphisms $f : x \rightarrow y$ and $g : y \rightarrow z$, $F(g \circ f) = F(g) \circ F(f).$

A **contravariant** functor $F{:} C \rightarrow D$, is like a covariant functor, except that it "turns morphisms around" ("reverses all the arrows"). More specifically, every morphism $f : x \rightarrow y$ in C must be assigned to a morphism $F(f) : F(y) \rightarrow F(x)$ in D. In other words, a contravariant functor is a covariant functor from the opposite category C^{op} to D.

Natural transformations and isomorphisms

A *natural transformation* is a relation between two functors. Functors often describe "natural constructions" and natural transformations then describe "natural homomorphisms" between two such constructions. Sometimes two quite different constructions yield "the same" result; this is expressed by a natural isomorphism between the two functors.

If F and G are (covariant) functors between the categories C and D, then a natural transformation from F to G associates to every object x in C a morphism $\eta_x : F(x) \rightarrow G(x)$ in D such that for every morphism $f : x \rightarrow y$ in C, we have $\eta_y \circ F(f) = G(f) \circ \eta_x$; this means that the following diagram is commutative:

$$F(X) \xrightarrow{\quad F(f) \quad} F(Y)$$
$$\eta_X \downarrow \qquad\qquad \downarrow \eta_Y$$
$$G(X) \xrightarrow[\quad G(f) \quad]{} G(Y)$$

The two functors *F* and *G* are called *naturally isomorphic* if there exists a natural transformation from *F* to *G* such that η_x is an isomorphism for every object *x* in *C*.

Universal constructions, limits, and colimits

Using the language of category theory, many areas of mathematical study can be cast into appropriate categories, such as the categories of all sets, groups, topologies, and so on. These categories surely have some objects that are "special" in a certain way, such as the empty set or the product of two topologies, yet in the definition of a category, objects are considered to be atomic, i.e., we *do not know* whether an object *A* is a set, a topology, or any other abstract concept – hence, the challenge is to define special objects without referring to the internal structure of those objects. But how can we define the empty set without referring to elements, or the product topology without referring to open sets?

The solution is to characterize these objects in terms of their relations to other objects, as given by the morphisms of the respective categories. Thus, the task is to find *universal properties* that uniquely determine the objects of interest. Indeed, it turns out that numerous important constructions can be described in a purely categorical way. The central concept which is needed for this purpose is called categorical *limit*, and can be dualized to yield the notion of a *colimit*.

Equivalent categories

It is a natural question to ask: under which conditions can two categories be considered to be "essentially the same", in the sense that theorems about one category can readily be transformed into theorems about the other category? The major tool one employs to describe such a situation is called *equivalence of categories*, which is given by appropriate functors between two categories. Categorical equivalence has found numerous applications in mathematics.

Further concepts and results

The definitions of categories and functors provide only the very basics of categorical algebra; additional important topics are listed below. Although there are strong interrelations between all of these topics, the given order can be considered as a guideline for further reading.

- The functor category D^C has as objects the functors from C to D and as morphisms the natural transformations of such functors. The Yoneda lemma is one of the most famous basic results of category theory; it describes representable functors in functor categories.
- Duality: Every statement, theorem, or definition in category theory has a *dual* which is essentially obtained by "reversing all the arrows". If one statement is true in a category C then its dual will be true in the dual category C^{op}. This duality, which is transparent at the level of category theory, is often obscured in applications and can lead to surprising relationships.
- Adjoint functors: A functor can be left (or right) adjoint to another functor that maps in the opposite direction. Such a pair of adjoint functors typically arises from a construction defined by a universal property; this can be seen as a more abstract and powerful view on universal properties.

Higher-dimensional categories

Many of the above concepts, especially equivalence of categories, adjoint functor pairs, and functor categories, can be situated into the context of *higher-dimensional categories*. Briefly, if we consider a morphism between two objects as a "process taking us from one object to another", then higher-dimensional categories allow us to profitably generalize this by considering "higher-dimensional processes".

For example, a (strict) 2-category is a category together with "morphisms between morphisms", i.e., processes which allow us to transform one morphism into another. We can then "compose" these "bimorphisms" both horizontally and vertically, and we require a 2-dimensional "exchange law" to hold, relating the two composition laws. In this context, the standard example is **Cat**, the 2-category of all (small) categories, and in this example, bimorphisms of morphisms are simply natural transformations of morphisms in the usual sense. Another basic example is to consider a 2-category with a single object; these are essentially monoidal categories. Bicategories are a weaker notion of 2-dimensional categories in which the composition of morphisms is not strictly associative, but only associative "up to" an isomorphism.

This process can be extended for all natural numbers n, and these are called n-categories. There is even a notion of *ω-category* corresponding to the ordinal number ω.

Higher-dimensional categories are part of the broader mathematical field of higher-dimensional algebra, a concept introduced by Ronald Brown. For a conversational introduction to these ideas, see John Baez, 'A Tale of n-categories' (1996). [3]

See also

- List of category theory topics
- Important publications in category theory
- Glossary of category theory
- Domain theory
- Enriched category theory
- Higher category theory
- Timeline of category theory and related mathematics
- Higher-dimensional algebra

Notes

[1] http://planetphysics.org/encyclopedia/FundamentalGroupoidFunctor.html
[2] Note that a morphism that is both epic and monic is not necessarily an isomorphism! For example, in the category consisting of two objects A and B, the identity morphisms, and a single morphism f from A to B, f is both epic and monic but is not an isomorphism.
[3] http://math.ucr.edu/home/baez/week73.html

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External links

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- Homepage of the Categories mailing list, (http://www.mta.ca/~cat-dist/categories.html) with extensive resource list.
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- Category Theory (http://planetmath.org/?op=getobj&from=objects&id=5622) on PlanetMath
- Categories, Logic and the Foundations of Physics (http://categorieslogicphysics.wikidot.com/), Webpage dedicated to the use of Categories and Logic in the Foundations of Physics.

- Interactive Web page (http://www.j-paine.org/cgi-bin/webcats/webcats.php) which generates examples of categorical constructions in the category of finite sets. Written by Jocelyn Paine (http://www.j-paine.org/)

Algebraic topology

Algebraic topology is a branch of mathematics which uses tools from abstract algebra to study topological spaces. The basic goal is to find algebraic invariants that classify topological spaces up to homeomorphism. In many situations this is too much to hope for and it is more prudent to aim for a more modest goal, classification up to homotopy equivalence.

Although algebraic topology primarily uses algebra to study topological problems, the converse, using topology to solve algebraic problems, is sometimes also possible. Algebraic topology, for example, allows for a convenient proof that any subgroup of a free group is again a free group.

The method of algebraic invariants

An older name for the subject was combinatorial topology, implying an emphasis on how a space X was constructed from simpler ones (the modern standard tool for such construction is the CW-complex). The basic method now applied in algebraic topology is to investigate spaces via algebraic invariants by mapping them, for example, to groups which have a great deal of manageable structure in a way that respects the relation of homeomorphism (or more general homotopy) of spaces. This allows one to recast statements about topological spaces into statements about groups, which are often easier to prove.

Two major ways in which this can be done are through fundamental groups, or more generally homotopy theory, and through homology and cohomology groups. The fundamental groups give us basic information about the structure of a topological space, but they are often nonabelian and can be difficult to work with. The fundamental group of a (finite) simplicial complex does have a finite presentation.

Homology and cohomology groups, on the other hand, are abelian and in many important cases finitely generated. Finitely generated abelian groups are completely classified and are particularly easy to work with.

Setting in category theory

In general, all constructions of algebraic topology are functorial; the notions of category, functor and natural transformation originated here. Fundamental groups and homology and cohomology groups are not only *invariants* of the underlying topological space, in the sense that two topological spaces which are homeomorphic have the same associated groups, but their associated morphisms also correspond — a continuous mapping of spaces induces a group homomorphism on the associated groups, and these homomorphisms can be used to show non-existence (or, much more deeply, existence) of mappings.

Results on homology

Several useful results follow immediately from working with finitely generated abelian groups. The free rank of the n-th homology group of a simplicial complex is equal to the n-th Betti number, so one can use the homology groups of a simplicial complex to calculate its Euler-Poincaré characteristic. As another example, the top-dimensional integral homology group of a closed manifold detects orientability: this group is isomorphic to either the integers or 0, according as the manifold is orientable or not. Thus, a great deal of topological information is encoded in the homology of a given topological space.

Beyond simplicial homology, which is defined only for simplicial complexes, one can use the differential structure of smooth manifolds via de Rham cohomology, or Čech or sheaf cohomology to investigate the solvability of differential equations defined on the manifold in question. De Rham showed that all of these approaches were interrelated and that, for a closed, oriented manifold, the Betti numbers derived through simplicial homology were the same Betti numbers as those derived through de Rham cohomology. This was extended in the 1950s, when Eilenberg and Steenrod generalized this approach. They defined homology and cohomology as functors equipped with natural transformations subject to certain axioms (e.g., a weak equivalence of spaces passes to an isomorphism of homology groups), verified that all existing (co)homology theories satisfied these axioms, and then proved that such an axiomatization uniquely characterized the theory.

Applications of algebraic topology

Classic applications of algebraic topology include:

- The Brouwer fixed point theorem: every continuous map from the unit n-disk to itself has a fixed point.
- The n-sphere admits a nowhere-vanishing continuous unit vector field if and only if n is odd. (For $n=2$, this is sometimes called the "hairy ball theorem".)
- The Borsuk-Ulam theorem: any continuous map from the n-sphere to Euclidean n-space identifies at least one pair of antipodal points.
- Any subgroup of a free group is free. This result is quite interesting, because the statement is purely algebraic yet the simplest proof is topological. Namely, any free group G may be realized as the fundamental group of a graph X. The main theorem on covering spaces tells us that every subgroup H of G is the fundamental group of some covering space Y of X; but every such Y is again a graph. Therefore its fundamental group H is free.
- Topological combinatorics

Notable algebraic topologists

- Karol Borsuk
- Luitzen Egbertus Jan Brouwer
- Ronald Brown (mathematician)
- Nicolas Bourbaki
- Jean Dieudonné
- Otto Hermann Künneth
- Charles Ehresmann
- Samuel Eilenberg
- Peter Freyd
- Alexander Grothendieck
- Heinz Hopf
- Saunders Mac Lane
- J. H. C. Whitehead
- Witold Hurewicz
- Egbert van Kampen
- William Lawvere
- J.P. May
- Barry Mitchell (mathematician)
- Grigori Perelman
- Nicolae Popescu
- Daniel Quillen
- Robert Rosen
- Jean-Pierre Serre
- Dennis Sullivan
- J.A. Zilber

Important theorems in algebraic topology

- Borsuk-Ulam theorem
- Brouwer fixed point theorem
- Cellular approximation theorem
- Eilenberg–Zilber theorem
- Hurewicz theorem
- Kunneth theorem
- Poincaré duality theorem
- Universal coefficient theorem
- Van Kampen's theorem
- Generalized van Kampen's theorems [1]
- Higher homotopy, generalized van Kampen's theorem[2]
- Whitehead's theorem

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- Ronald Brown, Philip J. Higgins and Rafael Sivera. 2008. Higher dimensional, higher homotopy, generalized van Kampen Theorem., in *Nonabelian Algebraic Topology: Higher homotopy groupoids of filtered spaces.* Part III. 512 pp, (Preprint). [4][5]
- Ronald Brown, *Topology and groupoids* [6] (2006) Booksurge LLC ISBN 1-4196-2722-8 .

See also

- Important publications in algebraic topology
- GNUL Textbook on Algebraic Topology vol.1 [7][8]
- Higher dimensional algebra
- Higher category theory
- Van Kampen's theorem
- Groupoid
- Lie groupoid
- Lie algebroid
- Grothendieck topology
- Serre spectral sequence
- Sheaf
- Homotopy
- Homotopy theory
- Fundamental group
- Homology theory
- Homological algebra
- Cohomology theory
- K-theory
- Algebraic K-theory
- TQFT
- Homotopy quantum field theory(HQFT)
- CW complex
- Simplicial complex
- Homology complex
- Algebroid
- Exact sequence

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Algebraic logic

In mathematical logic, **algebraic logic** is the study of logic presented in an algebraic style.

Algebras as models of logics

Algebraic logic treats algebraic structures, often bounded lattices, as models (interpretations) of certain logics, making logic a branch of order theory.

In algebraic logic:

- Variables are tacitly universally quantified over some universe of discourse. There are no existentially quantified variables or open formulas;
- Terms are built up from variables using primitive and defined operations. There are no connectives;
- Formulas, built from terms in the usual way, can be equated if they are logically equivalent. To express a tautology, equate a formula with a truth value;
- The rules of proof are the substitution of equals for equals, and uniform replacement. Modus ponens remains valid, but is seldom employed.

In the table below, the left column contains one or more logical or mathematical systems, and the algebraic structure which are its models are shown on the right in the same row. Some of these structures are either Boolean algebras or proper extensions thereof. Modal and other nonclassical logics are typically modeled by what are called "Boolean algebras with operators."

Algebraic formalisms going beyond first-order logic in at least some respects include:

- Combinatory logic, having the expressive power of set theory;
- Relation algebra, arguably the paradigmatic algebraic logic, can express Peano arithmetic and most axiomatic set theories, including the canonical ZFC.

logical system	its models
Classical sentential logic	Lindenbaum-Tarski algebra Two-element Boolean algebra
Intuitionistic propositional logic	Heyting algebra
Łukasiewicz logic	MV-algebra
Modal logic K	Modal algebra
Lewis's S4	Interior algebra
Lewis's S5; Monadic predicate logic	Monadic Boolean algebra
First-order logic	Cylindric algebra Polyadic algebra Predicate functor logic
Set theory	Combinatory logic Relation algebra

History

On the history of algebraic logic before World War II, see Brady (2000) and Grattan-Guinness (2000) and their ample references. On the postwar history, see Maddux (1991) and Quine (1976).

Algebraic logic has at least two meanings:

- The study of Boolean algebra, begun by George Boole, and of relation algebra, begun by Augustus DeMorgan, extended by Charles Sanders Peirce, and taking definitive form in the work of Ernst Schröder;
- Abstract algebraic logic, a branch of contemporary mathematical logic.

Perhaps surprisingly, algebraic logic is the oldest approach to formal logic, arguably beginning with a number of memoranda Leibniz wrote in the 1680s, some of which were published in the 19th century and translated into English by Clarence Lewis in 1918. But nearly all of Leibniz's known work on algebraic logic was published only in 1903, after Louis Couturat discovered it in Leibniz's Nachlass. Parkinson (1966) and Loemker (1969) translated selections from Couturat's volume into English.

Brady (2000) discusses the rich historical connections between algebraic logic and model theory. The founders of model theory, Ernst Schroder and Leopold Loewenheim, were logicians in the algebraic tradition. Alfred Tarski, the founder of set theoretic model theory as a major branch of contemporary mathematical logic, also:

- Co-discovered Lindenbaum-Tarski algebra;
- Invented cylindric algebra;
- Wrote the 1940 paper that revived relation algebra, and that can be seen as the starting point of abstract algebraic logic.

Modern mathematical logic began in 1847, with two pamphlets whose respective authors were Augustus DeMorgan and George Boole. They, and later C.S. Peirce, Hugh MacColl, Frege, Peano, Bertrand Russell, and A. N. Whitehead all shared Leibniz's dream of combining symbolic logic, mathematics, and philosophy. Relation algebra is arguably the culmination of Leibniz's approach to logic. With the exception of some writings by Leopold Loewenheim and Thoralf Skolem, algebraic logic went into eclipse soon after the 1910-13 publication of *Principia Mathematica*, not to revive until Tarski's 1940 reexposition of relation algebra.

Leibniz had no influence on the rise of algebraic logic because his logical writings were little studied before the Parkinson and Loemker translations. Our present understanding of Leibniz the logician stems mainly from the work of Wolfgang Lenzen, summarized in Lenzen (2004). [1] To see how present-day work in logic and metaphysics can draw inspiration from, and shed light on, Leibniz's thought, see Zalta (2000). [2]

See also

- Abstract algebraic logic
- Algebraic structure
- Boolean algebra (logic)
- Boolean algebra (structure)
- Cylindric algebra
- Lindenbaum-Tarski algebra
- Mathematical logic
- Model theory
- Monadic Boolean algebra
- Predicate functor logic
- Relation algebra
- Universal algebra

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External links

- Stanford Encyclopedia of Philosophy: "Propositional Consequence Relations and Algebraic Logic [6]" -- by Ramon Jansana.

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[5] http://mally.stanford.edu/leibniz.pdf
[6] http://plato.stanford.edu/entries/consequence-algebraic/

Quantum logic

In quantum mechanics, **quantum logic** is a set of rules for reasoning about propositions which takes the principles of quantum theory into account. This research area and its name originated in the 1936 paper by Garrett Birkhoff and John von Neumann, who were attempting to reconcile the apparent inconsistency of classical boolean logic with the facts concerning the measurement of complementary variables in quantum mechanics, such as position and momentum.

Quantum logic can be formulated either as a modified version of propositional logic or as a non-commutative and non-associative many-valued (MV) logic[1] [2] [3] [4] [5]. It has some properties which clearly distinguish it from classical logic, most notably, the failure of the distributive law of propositional logic:

> *p* and (*q* or *r*) = (*p* and *q*) or (*p* and *r*),

where the symbols *p*, *q* and *r* are propositional variables. To illustrate why the distributive law fails, consider a particle moving on a line and let

> *p* = "the particle is moving to the right"

> *q* = "the particle is in the interval [-1,1]"

> *r* = "the particle is not in the interval [-1,1]"

then the proposition "*q* or *r*" is true, so

> *p* and (*q* or *r*) = *p*

On the other hand, the propositions "*p* and *q*" and "*p* and *r*" are both false, since they assert tighter restrictions on simultaneous values of position and momentum than is allowed by the uncertainty principle. So,

> (*p* and *q*) or (*p* and *r*) = false

Thus the distributive law fails.

Quantum logic has been proposed as the correct logic for propositional inference generally, most notably by the philosopher Hilary Putnam, at least at one point in his career. This thesis was an important ingredient in Putnam's paper *Is Logic Empirical?* in which he analysed the epistemological status of the rules of propositional logic. Putnam attributes the idea that anomalies associated to quantum measurements originate with anomalies in the logic of physics itself to the physicist David Finkelstein. It should be noted, however, that this idea had been around for some time and had been revived several years earlier by George Mackey's work on group representations and symmetry.

The more common view regarding quantum logic, however, is that it provides a formalism for relating observables, system preparation filters and states. In this view, the quantum logic approach resembles more closely the C*-algebraic approach to quantum mechanics; in fact with some minor technical assumptions it can be subsumed by it. The similarities of the quantum logic formalism to a system of deductive logic may then be regarded more as a curiosity than as a fact of fundamental philosophical importance.

Introduction

In his classic treatise *Mathematical Foundations of Quantum Mechanics*, John von Neumann noted that projections on a Hilbert space can be viewed as propositions about physical observables. The set of principles for manipulating these quantum propositions was called *quantum logic* by von Neumann and Birkhoff. In his book (also called *Mathematical Foundations of Quantum Mechanics*) G. Mackey attempted to provide a set of axioms for this propositional system as an orthocomplemented lattice. Mackey viewed elements of this set as potential *yes or no questions* an observer might ask about the state of a physical system, questions that would be settled by some measurement. Moreover Mackey defined a physical observable in terms of these basic questions. Mackey's axiom system is somewhat unsatisfactory though, since it assumes that the partially ordered set is actually given as the orthocomplemented closed subspace lattice of a separable Hilbert space. Piron, Ludwig and others have attempted to give axiomatizations which do not require such explicit relations to the lattice of subspaces.

The remainder of this article assumes the reader is familiar with the spectral theory of self-adjoint operators on a Hilbert space. However, the main ideas can be understood using the finite-dimensional spectral theorem.

Projections as propositions

The so-called *Hamiltonian* formulations of classical mechanics have three ingredients: *states*, *observables* and *dynamics*. In the simplest case of a single particle moving in $\mathbf{R}^3$, the state space is the position-momentum space $\mathbf{R}^6$. We will merely note here that an observable is some real-valued function f on the state space. Examples of observables are position, momentum or energy of a particle. For classical systems, the value $f(x)$, that is the value of f for some particular system state x, is obtained by a process of measurement of f. The propositions concerning a classical system are generated from basic statements of the form

- Measurement of f yields a value in the interval $[a, b]$ for some real numbers a, b.

It follows easily from this characterization of propositions in classical systems that the corresponding logic is identical to that of some Boolean algebra of subsets of the state space. By logic in this context we mean the rules that relate set operations and ordering relations, such as de Morgan's laws. These are analogous to the rules relating boolean conjunctives and material implication in classical propositional logic. For technical reasons, we will also assume that the algebra of subsets of the state space is that of all Borel sets. The set of propositions is ordered by the natural ordering of sets and has a complementation operation. In terms of observables, the complement of the proposition $\{f \geq a\}$ is $\{f < a\}$.

We summarize these remarks as follows:

- The proposition system of a classical system is a lattice with a distinguished *orthocomplementation* operation: The lattice operations of *meet* and *join* are respectively set intersection and set union. The orthocomplementation operation is set complement. Moreover this lattice is *sequentially complete*, in the sense that any sequence $\{E_i\}_i$ of elements of the lattice has a least upper bound, specifically the set-theoretic union:

$$\mathrm{LUB}(\{E_i\}) = \bigcup_{i=1}^{\infty} E_i.$$

In the Hilbert space formulation of quantum mechanics as presented by von Neumann, a physical observable is represented by some (possibly unbounded) densely-defined self-adjoint operator A on a Hilbert space H. A has a spectral decomposition, which is a projection-valued measure E defined on the Borel subsets of **R**. In particular, for any bounded Borel function f, the following equation holds:

$$f(A) = \int_{\mathbb{R}} f(\lambda)\, d\mathrm{E}(\lambda).$$

In case f is the indicator function of an interval $[a, b]$, the operator $f(A)$ is a self-adjoint projection, and can be interpreted as the quantum analogue of the classical proposition

- Measurement of A yields a value in the interval $[a, b]$.

The propositional lattice of a quantum mechanical system

This suggests the following quantum mechanical replacement for the orthocomplemented lattice of propositions in classical mechanics. This is essentially Mackey's *Axiom VII*:

- The orthocomplemented lattice Q of propositions of a quantum mechanical system is the lattice of closed subspaces of a complex Hilbert space H where orthocomplementation of V is the orthogonal complement $V^{\Box}$.

Q is also sequentially complete: any pairwise disjoint sequence $\{V_i\}_i$ of elements of Q has a least upper bound. Here disjointness of W_1 and W_2 means W_2 is a subspace of $W_1^{\Box}$. The least upper bound of $\{V_i\}_i$ is the closed internal direct sum.

Henceforth we identify elements of Q with self-adjoint projections on the Hilbert space H.

The structure of Q immediately points to a difference with the partial order structure of a classical proposition system. In the classical case, given a proposition p, the equations

$$I = p \vee q$$
$$0 = p \wedge q$$

have exactly one solution, namely the set-theoretic complement of p. In these equations I refers to the atomic proposition which is identically true and 0 the atomic proposition which is identically false. In the case of the lattice of projections there are infinitely many solutions to the above equations.

Having made these preliminary remarks, we turn everything around and attempt to define observables within the projection lattice framework and using this definition establish the correspondence between self-adjoint operators and observables : A *Mackey observable* is a countably additive homomorphism from the orthocomplemented lattice of the Borel subsets of **R** to Q. To say the mapping φ is a countably additive homomorphism means that for any sequence $\{S_i\}_i$ of pairwise disjoint Borel subsets of **R**, $\{\varphi(S_i)\}_i$ are pairwise orthogonal projections and

$$\varphi\left(\bigcup_{i=1}^{\infty} S_i\right) = \sum_{i=1}^{\infty} \varphi(S_i).$$

Theorem. There is a bijective correspondence between Mackey observables and densely-defined self-adjoint operators on H.

This is the content of the spectral theorem as stated in terms of spectral measures.

Statistical structure

Imagine a forensics lab which has some apparatus to measure the speed of a bullet fired from a gun. Under carefully controlled conditions of temperature, humidity, pressure and so on the same gun is fired repeatedly and speed measurements taken. This produces some distribution of speeds. Though we will not get exactly the same value for each individual measurement, for each cluster of measurements, we would expect the experiment to lead to the same distribution of speeds. In particular, we can expect to assign probability distributions to propositions such as $\{a \leq \text{speed} \leq b\}$. This leads naturally to propose that under controlled conditions of preparation, the measurement of a classical system can be described by a probability measure on the state space. This same statistical structure is also present in quantum mechanics.

A *quantum probability measure* is a function P defined on Q with values in [0,1] such that P(0)=0, P(I)=1 and if $\{E_i\}_i$ is a sequence of pairwise orthogonal elements of Q then

$$\mathrm{P}\left(\sum_{i=1}^{\infty} E_i\right) = \sum_{i=1}^{\infty} \mathrm{P}(E_i).$$

The following highly non-trivial theorem is due to Andrew Gleason:

Theorem. Suppose H is a separable Hilbert space of complex dimension at least 3. Then for any quantum probability measure on Q there exists a unique trace class operator S such that

$$\mathrm{P}(E) = \mathrm{Tr}(SE)$$

for any self-adjoint projection E.

The operator S is necessarily non-negative (that is all eigenvalues are non-negative) and of trace 1. Such an operator is often called a *density operator*.

Physicists commonly regard a density operator as being represented by a (possibly infinite) density matrix relative to some orthonormal basis.

For more information on statistics of quantum systems, see quantum statistical mechanics.

Automorphisms

An *automorphism* of Q is a bijective mapping $\alpha:Q \rightarrow Q$ which preserves the orthocomplemented structure of Q, that is

$$\alpha\left(\sum_{i=1}^{\infty} E_i\right) = \sum_{i=1}^{\infty} \alpha(E_i)$$

for any sequence $\{E_i\}_i$ of pairwise orthogonal self-adjoint projections. Note that this property implies monotonicity of α. If P is a quantum probability measure on Q, then $E \rightarrow \alpha(E)$ is also a quantum probability measure on Q. By the Gleason theorem characterizing quantum probability measures quoted above, any automorphism α induces a mapping $\alpha*$ on the density operators by the following formula:

$$\mathrm{Tr}(\alpha^*(S)E) = \mathrm{Tr}(S\alpha(E)).$$

The mapping $\alpha*$ is bijective and preserves convex combinations of density operators. This means

$$\alpha^*(r_1 S_1 + r_2 S_2) = r_1 \alpha^*(S_1) + r_2 \alpha^*(S_2)$$

whenever $1 = r_1 + r_2$ and r_1, r_2 are non-negative real numbers. Now we use a theorem of Richard Kadison:

Theorem. Suppose β is a bijective map from density operators to density operators which is convexity preserving. Then there is an operator *U* on the Hilbert space which is either linear or conjugate-linear, preserves the inner product and is such that

$$\beta(S) = USU^*$$

for every density operator *S*. In the first case we say *U* is unitary, in the second case *U* is anti-unitary.

> **Remark**. This note is included for technical accuracy only, and should not concern most readers. The result quoted above is not directly stated in Kadison's paper, but can be reduced to it by noting first that β extends to a positive trace preserving map on the trace class operators, then applying duality and finally applying a result of Kadison's paper.

The operator *U* is not quite unique; if *r* is a complex scalar of modulus 1, then r *U* will be unitary or anti-unitary if *U* is and will implement the same automorphism. In fact, this is the only ambiguity possible.

It follows that automorphisms of *Q* are in bijective correspondence to unitary or anti-unitary operators modulo multiplication by scalars of modulus 1. Moreover, we can regard automorphisms in two equivalent ways: as operating on states (represented as density operators) or as operating on *Q*.

Non-relativistic dynamics

In non-relativistic physical systems, there is no ambiguity in referring to time evolution since there is a global time parameter. Moreover an isolated quantum system evolves in a deterministic way: if the system is in a state *S* at time *t* then at time *s* > *t*, the system is in a state $F_{s,t}(S)$. Moreover, we assume

- The dependence is reversible: The operators $F_{s,t}$ are bijective.
- The dependence is homogeneous: $F_{s,t} = F_{s-t,0}$.
- The dependence is convexity preserving: That is, each $F_{s,t}(S)$ is convexity preserving.
- The dependence is weakly continuous: The mapping **R**→ **R** given by $t \to \text{Tr}(F_{s,t}(S)\,E)$ is continuous for every *E* in *Q*.

By Kadison's theorem, there is a 1-parameter family of unitary or anti-unitary operators $\{U_t\}_t$ such that

$$F_{s,t}(S) = U_{s-t}SU^*_{s-t}$$

In fact,

Theorem. Under the above assumptions, there is a strongly continuous 1-parameter group of unitary operators $\{U_t\}_t$ such that the above equation holds.

Note that it easily from uniqueness from Kadison's theorem that

$$U_{t+s} = \sigma(t,s)U_tU_s$$

where σ(t,s) has modulus 1. Now the square of an anti-unitary is a unitary, so that all the U_t are unitary. The remainder of the argument shows that σ(t,s) can be chosen to be 1 (by modifying each U_t by a scalar of modulus 1.)

Pure states

A convex combinations of statistical states S_1 and S_2 is a state of the form $S = p_1 S_1 + p_2 S_2$ where p_1, p_2 are non-negative and $p_1 + p_2 = 1$. Considering the statistical state of system as specified by lab conditions used for its preparation, the convex combination S can be regarded as the state formed in the following way: toss a biased coin with outcome probabilities p_1, p_2 and depending on outcome choose system prepared to S_1 or S_2

Density operators form a convex set. The convex set of density operators has extreme points; these are the density operators given by a projection onto a one-dimensional space. To see that any extreme point is such a projection, note that by the spectral theorem S can be represented by a diagonal matrix; since S is non-negative all the entries are non-negative and since S has trace 1, the diagonal entries must add up to 1. Now if it happens that the diagonal matrix has more than one non-zero entry it is clear that we can express it as a convex combination of other density operators.

The extreme points of the set of density operators are called pure states. If S is the projection on the 1-dimensional space generated by a vector ψ of norm 1 then

$$\mathrm{Tr}(SE) = \langle E\psi|\psi\rangle$$

for any E in Q. In physics jargon, if

$$S = |\psi\rangle\langle\psi|,$$

where ψ has norm 1, then

$$\mathrm{Tr}(SE) = \langle\psi|E|\psi\rangle.$$

Thus pure states can be identified with *rays* in the Hilbert space H.

The measurement process

Consider a quantum mechanical system with lattice Q which is in some statistical state given by a density operator S. This essentially means an ensemble of systems specified by a repeatable lab preparation process. The result of a cluster of measurements intended to determine the truth value of proposition E, is just as in the classical case, a probability distribution of truth values **T** and **F**. Say the probabilities are p for **T** and $q = 1 - p$ for **F**. By the previous section $p = \mathrm{Tr}(S\,E)$ and $q = \mathrm{Tr}(S\,(I\text{-}E))$.

Perhaps the most fundamental difference between classical and quantum systems is the following: regardless of what process is used to determine E immediately after the measurement the system will be in one of two statistical states:

- If the result of the measurement is **T**

$$\frac{1}{\mathrm{Tr}(ES)}ESE.$$

- If the result of the measurement is **F**

$$\frac{1}{\mathrm{Tr}((I-E)S)}(I-E)S(I-E).$$

(We leave to the reader the handling of the degenerate cases in which the denominators may be 0.) We now form the convex combination of these two ensembles using the relative frequencies p and q. We thus obtain the result that the measurement process applied to a statistical ensemble in state S yields another ensemble in statistical state:

$$\mathrm{M}_E(S) = ESE + (I-E)S(I-E).$$

We see that a pure ensemble becomes a mixed ensemble after measurement. Measurement, as described above, is a special case of quantum operations.

Limitations

Quantum logic derived from propositional logic provides a satisfactory foundation for a theory of reversible quantum processes. Examples of such processes are the covariance transformations relating two frames of reference, such as change of time parameter or the transformations of special relativity. Quantum logic also provides a satisfactory understanding of density matrices. Quantum logic can be stretched to account for some kinds of measurement processes corresponding to answering yes-no questions about the state of a quantum system. However, for more general kinds of measurement operations (that is quantum operations), a more complete theory of filtering processes is necessary. Such an approach is provided by the consistent histories formalism. On the other hand, quantum logics derived from MV-logic extend its range of applicability to irreversible quantum processes and/or 'open' quantum systems.

In any case, these quantum logic formalisms must be generalized in order to deal with super-geometry (which is needed to handle Fermi-fields) and non-commutative geometry (which is needed in string theory and quantum gravity theory). Both of these theories use a partial algebra with an "integral" or "trace". The elements of the partial algebra are not observables; instead the "trace" yields "greens functions" which generate scattering amplitudes. One thus obtains a local S-matrix theory (see D. Edwards).

Since around 1978 the Flato school (see F. Bayen) has been developing an alternative to the quantum logics approach called deformation quantization (see Weyl quantization).

In 2004, Prakash Panangaden described how to capture the kinematics of quantum causal evolution using System BV, a deep inference logic originally developed for use in structural proof theory.[6] Alessio Guglielmi, Lutz Straßburger, and Richard Blute have also done work in this area.[7]

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See also

- Mathematical formulation of quantum mechanics
- Multi-valued logic
- Quasi-set theory
- HPO formalism (An approach to temporal quantum logic)
- Quantum field theory

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External links

- Stanford Encyclopedia of Philosophy entry on Quantum Logic and Probability Theory (http://plato.stanford.edu/entries/qt-quantlog/)

Lukasiewicz logic

1. REDIRECT Łukasiewicz logic

MV-algebra

In abstract algebra, a branch of pure mathematics, an **MV-algebra** is an algebraic structure with a binary operation $\oplus$, a unary operation $\neg$, and the constant 0, satisfying certain axioms. MV-algebras are models of Łukasiewicz logic; the letters MV refer to *multi-valued* logic of Łukasiewicz.

Definitions

An **MV-algebra** is an algebraic structure $\langle A, \oplus, \neg, 0 \rangle$, consisting of

- a non-empty set A,
- a binary operation $\oplus$ on A,
- a unary operation $\neg$ on A, and
- a constant 0 denoting a fixed element of A,

which satisfies the following identities:

- $(x \oplus y) \oplus z = x \oplus (y \oplus z)$,
- $x \oplus 0 = x$,
- $x \oplus y = y \oplus x$,
- $\neg\neg x = x$,
- $x \oplus \neg 0 = \neg 0$, and
- $\neg(\neg x \oplus y) \oplus y = \neg(\neg y \oplus x) \oplus x$.

By virtue of the first three axioms, $\langle A, \oplus, 0 \rangle$ is a commutative monoid. Being defined by identities, MV-algebras form a variety of algebras. The variety of MV-algebras is a subvariety of the variety of BL-algebras and contains all Boolean algebras.

An MV-algebra can equivalently be defined (Hájek 1998) as a prelinear commutative bounded integral residuated lattice $\langle L, \wedge, \vee, \otimes, \rightarrow, 0, 1 \rangle$ satisfying the additional identity $x \vee y = (x \rightarrow y) \rightarrow y$.

Examples of MV-algebras

A simple numerical example is $A = [0,1]$, with operations $x \oplus y = \min(x + y, 1)$ and $\neg x = 1 - x$. In mathematical fuzzy logic, this MV-algebra is called the *standard MV-algebra*, as it forms the standard real-valued semantics of Łukasiewicz logic.

The *trivial* MV-algebra has the only element 0 and the operations defined in the only possible way, $0 \oplus 0 = 0$ and $\neg 0 = 0$.

The *two-element* MV-algebra is actually the two-element Boolean algebra $\{0, 1\}$, with $\oplus$ coinciding with Boolean disjunction and $\neg$ with Boolean negation.

Other finite linearly ordered MV-algebras are obtained by restricting the universe and operations of the standard MV-algebra to the set of $n + 1$ equidistant real numbers between 0 and 1 (both included), that is, the set $\{0, 1/n, 2/n, \ldots, 1\}$, which is closed under the operations $\oplus$ and $\neg$ of the standard MV-algebra.

Another important example is *Chang's MV-algebra*, consisting just of infinitesimals (with the order type ω) and their co-infinitesimals.

Relation to Łukasiewicz logic

Chang devised MV-algebras to study multi-valued logics, introduced by Jan Łukasiewicz in 1920. In particular, MV-algebras form the algebraic semantics of Łukasiewicz logic, as described below.

Given an MV-algebra *A*, an *A*-valuation is a homomorphism from the algebra of propositional formulas (in the language consisting of $\oplus, \neg,$ and 0) into *A*. Formulas mapped to 1 (or $\neg 0$) for all *A*-valuations are called *A*-tautologies. If the standard MV-algebra over [0,1] is employed, the set of all [0,1]-tautologies determines so-called infinite-valued Łukasiewicz logic.

Chang's (1958, 1959) completeness theorem states that any MV-algebra equation holding in the standard MV-algebra over the interval [0,1] will hold in every MV-algebra. Algebraically, this means that the standard MV-algebra generates the variety of all MV-algebras. Equivalently, Chang's completeness theorem says that MV-algebras characterize infinite-valued Łukasiewicz logic, defined as the set of [0,1]-tautologies.

The way the [0,1] MV-algebra characterizes all possible MV-algebras parallels the well-known fact that identities holding in the two-element Boolean algebra hold in all possible Boolean algebras. Moreover, MV-algebras characterize infinite-valued Łukasiewicz logic in a manner analogous to the way that Boolean algebras characterize classical bivalent logic (see Lindenbaum-Tarski algebra).

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External links

- Stanford Encyclopedia of Philosophy: "Many-valued logic [1]" -- by Siegfried Gottwald.

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Biophysical Chemistry Applications

Molecular evolution

Molecular evolution is the process of evolution at the scale of DNA, RNA, and proteins. Molecular evolution emerged as a scientific field in the 1960s as researchers from molecular biology, evolutionary biology and population genetics sought to understand recent discoveries on the structure and function of nucleic acids and protein. Some of the key topics that spurred development of the field have been the evolution of enzyme function, the use of nucleic acid divergence as a "molecular clock" to study species divergence, and the origin of non-functional or junk DNA. Recent advances in genomics, including whole-genome sequencing, high-throughput protein characterization, and bioinformatics have led to a dramatic increase in studies on the topic. In the 2000s, some of the active topics have been the role of gene duplication in the emergence of novel gene function, the extent of adaptive molecular evolution versus neutral drift, and the identification of molecular changes responsible for various human characteristics especially those pertaining to infection, disease, and cognition.

Principles of molecular evolution

Mutations

Mutations are permanent, transmissible changes to the genetic material (usually DNA or RNA) of a cell. Mutations can be caused by copying errors in the genetic material during cell division and by exposure to radiation, chemicals, or viruses, or can occur deliberately under cellular control during the processes such as meiosis or hypermutation. Mutations are considered the driving force of evolution, where less favorable (or *deleterious*) mutations are removed from the gene pool by natural selection, while more favorable (or *beneficial*) ones tend to accumulate. Neutral mutations do not affect the organism's chances of survival in its natural environment and can accumulate over time, which might result in what is known as punctuated equilibrium; the modern interpretation of classic evolutionary theory.

Causes of change in allele frequency

There are three known processes that affect the survival of a characteristic; or, more specifically, the frequency of an allele (variant of a gene):

- Genetic drift describes changes in gene frequency that cannot be ascribed to selective pressures, but are due instead to events that are unrelated to inherited traits. This is especially important in small mating populations, which simply cannot have enough offspring to maintain the same gene distribution as the parental generation.
- Gene flow or Migration: or gene admixture is the only one of the agents that makes populations closer genetically while building larger gene pools.
- Selection, in particular natural selection produced by differential mortality and fertility. Differential mortality is the survival rate of individuals before their reproductive age. If

they survive, they are then selected further by differential fertility – that is, their total genetic contribution to the next generation. In this way, the alleles that these surviving individuals contribute to the gene pool will increase the frequency of those alleles. Sexual selection, the attraction between mates that results from two genes, one for a feature and the other determining a preference for that feature, is also very important.

Molecular study of phylogeny

Molecular systematics is a product of the traditional field of systematics and molecular genetics. It is the process of using data on the molecular constitution of biological organisms' DNA, RNA, or both, in order to resolve questions in systematics, i.e. about their correct scientific classification or taxonomy from the point of view of evolutionary biology.

Molecular systematics has been made possible by the availability of techniques for DNA sequencing, which allow the determination of the exact sequence of nucleotides or *bases* in either DNA or RNA. At present it is still a long and expensive process to sequence the entire genome of an organism, and this has been done for only a few species. However, it is quite feasible to determine the sequence of a defined area of a particular chromosome. Typical molecular systematic analyses require the sequencing of around 1000 base pairs.

The driving forces of evolution

Depending on the relative importance assigned to the various forces of evolution, three perspectives provide evolutionary explanations for molecular evolution.[1]

While recognizing the importance of random drift for silent mutations,[2] **selectionists hypotheses** argue that balancing and positive selection are the driving forces of molecular evolution. Those hypotheses are often based on the broader view called panselectionism, the idea that selection is the only force strong enough to explain evolution, relaying random drift and mutations to minor roles.[1]

Neutralists hypotheses emphasize the importance of mutation, purifying selection and random genetic drift.[3] The introduction of the neutral theory by Kimura,[4] quickly followed by King and Jukes' own findings,[5] lead to a fierce debate about the relevance of neodarwinism at the molecular level. The Neutral theory of molecular evolution states that most mutations are deleterious and quickly removed by natural selection, but of the remaining ones, the vast majority are neutral with respect to fitness while the amount of advantageous mutations is vanishingly small. The fate of neutral mutations are governed by genetic drift, and contribute to both nucleotide polymorphism and fixed differences between species. [6] [7] [8]

Mutationists hypotheses emphasize random drift and biases in mutation patterns.[9] Sueoka was the first to propose a modern mutationist view. He proposed that the variation in GC content was not the result of positive selection, but a consequence of the GC mutational pressure.[10]

Related fields

An important area within the study of molecular evolution is the use of molecular data to determine the correct biological classification of organisms. This is called molecular systematics or molecular phylogenetics.

Tools and concepts developed in the study of molecular evolution are now commonly used for comparative genomics and molecular genetics, while the influx of new data from these fields has been spurring advancement in molecular evolution.

Key researchers in molecular evolution

Some researchers who have made key contributions to the development of the field:

- Motoo Kimura — Neutral theory
- Masatoshi Nei — Adaptive evolution
- Walter M. Fitch — Phylogenetic reconstruction
- Walter Gilbert — RNA world
- Joe Felsenstein — Phylogenetic methods
- Susumu Ohno — Gene duplication
- John H. Gillespie — Mathematics of adaptation

Journals and societies

Journals dedicated to molecular evolution include *Molecular Biology and Evolution*, *Journal of Molecular Evolution*, and *Molecular Phylogenetics and Evolution*. Research in molecular evolution is also published in journals of genetics, molecular biology, genomics, systematics, or evolutionary biology. The Society for Molecular Biology and Evolution [11] publishes the journal "Molecular Biology and Evolution" and holds an annual international meeting.

See also

- History of molecular evolution
- Chemical evolution
- Evolution
- Genetic drift
- *E. coli* long-term evolution experiment
- Evolutionary physiology
- Neutral theory of molecular evolution
- Nucleotide diversity
- Parsimony
- Population genetics
- Selection

- Genomic organization
- Horizontal gene transfer
- Human evolution
- Molecular clock
- Comparative phylogenetics

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[7] The nearly neutral theory expanded the neutralist perspective, suggesting that several mutations are nearly neutral, which means both random drift and natural selection is relevant to their dynamics.

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[11] http://www.smbe.org

Radiobiology

Radiobiology (or *radiation biology*) is the interdisciplinary field of science that studies the biological effects of ionizing and non-ionizing radiation of the whole electromagnetic spectrum, including radioactivity (alpha, beta and gamma), x-rays, ultraviolet radiation, visible light, microwaves, radio wave, low-frequency radiation (such as used in alternate electric transmission, ultrasound thermal radiation (heat), and related modalities. It is a subset of biophysics.

Areas of interest

The interactions between electromagnetic fields (EMF) and organisms can be studied at several levels:

- radiation physics
- radiation chemistry
- molecular and cell biology
- molecular genetics
- cell death and apoptosis
- dose modifying agents
- protection and repair mechanisms
- tissue responses to radiation
- high and low-level electromagnetic radiation and health
- specific absorption rates of organisms
- radiation poisoning
- radiation oncology (radiation therapy in cancer)

Radiobiology of non-ionizing radiation includes:

- Bioelectromagnetics
- Magnetobiology

Radiation sources for radiobiology

Radiobiology experiments typically make use of a radiation source which could be:

- An isotopic source, typically ^{137}Cs or ^{60}Co.
- A particle accelerator generating high energy protons, electrons or charged ions. Biological samples can be irradiated using either a broad, uniform beam or using a microbeam, focused down to cellular or subcellular sizes.
- A UV lamp.

See also

- Radiosensitivity
- Radiology
- Nuclear medicine
- Radioactivity in biology
- Radiophobia
- Cell survival curve
- Relative biological effectiveness

Notes

- WikiMindMap [1]

[1] http://www.wikimindmap.org/viewmap.php?wiki=en.wikipedia.org&topic=radiobiology

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Weblinks

- The Institute for Radiation Biology at the Helmholtz-Center for Environmental Health (http://www.helmholtz-muenchen.de/en/isb/isb-home/index.html)

Photosynthesis

Photosynthesis[α] is a process that converts carbon dioxide into organic compounds, especially sugars, using the energy from sunlight.[1] Photosynthesis occurs in plants, algae, and many species of Bacteria, but not in Archaea. Photosynthetic organisms are called *photoautotrophs*, since it allows them to create their own food. In plants, algae and cyanobacteria photosynthesis uses carbon dioxide and water, releasing oxygen as a

Composite image showing the global distribution of photosynthesis, including both oceanic phytoplankton and land vegetation.

waste product. Photosynthesis is vital for life on Earth. As well as maintaining the normal level of oxygen in the atmosphere, nearly all life either depends on it directly as a source of energy, or indirectly as the ultimate source of the energy in their food.[β][2] The amount of energy trapped by photosynthesis is immense, approximately 100 terawatts:[3] which is about six times larger than the power consumption of human civilization.[4] As well as energy, photosynthesis is also the source of the carbon in all the organic compounds within organisms' bodies. In all, photosynthetic organisms convert around 100,000,000,000 tonnes of carbon into biomass per year.[5]

Although photosynthesis can occur in different ways in different species, some features are always the same. For example, the process always begins when energy from light is absorbed by proteins called photosynthetic reaction centers that contain chlorophylls. In plants, these proteins are held inside organelles called chloroplasts, while in bacteria they are embedded in the plasma membrane. Some of the light energy gathered by chlorophylls is stored in the form of adenosine triphosphate (ATP). The rest of the energy is used to remove electrons from a substance such as water. These electrons are then used in the reactions that turn carbon dioxide into organic compounds. In plants, algae and cyanobacteria this is done by a sequence of reactions called the Calvin cycle, but different sets of reactions are found in some bacteria, such as the reverse Krebs cycle in *Chlorobium*. Many photosynthetic organisms have adaptations that concentrate or store carbon dioxide. This helps reduce a wasteful process called photorespiration that can consume part of the sugar produced during photosynthesis.
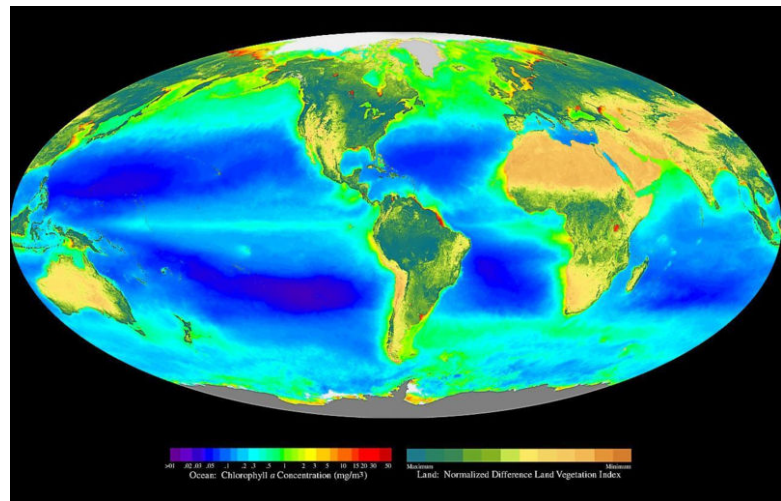
Photosynthesis evolved early in the evolutionary history of life, when all forms of life on Earth were microorganisms. The first photosynthetic organisms probably evolved about 3500 [6] million years ago, and used hydrogen or hydrogen sulfide as sources of electrons, rather than water.[7] Cyanobacteria appeared later, around 3000 [8] million years ago, and changed the Earth forever when they began to oxygenate the atmosphere, beginning about 2400 [9] million years ago.[10] This new atmosphere allowed the evolution of complex life such as protists. Eventually, about 550 [11] million years ago, one of these protists formed a symbiotic relationship with a cyanobacterium, producing the ancestor of the plants and algae.[12] The chloroplasts in modern plants are the descendants of these ancient symbiotic cyanobacteria.

Overview of cycle between autotrophs and heterotrophs. Photosynthesis is the main means by which plants, algae and many bacteria produce organic compounds and oxygen from carbon dioxide and water (green arrow).
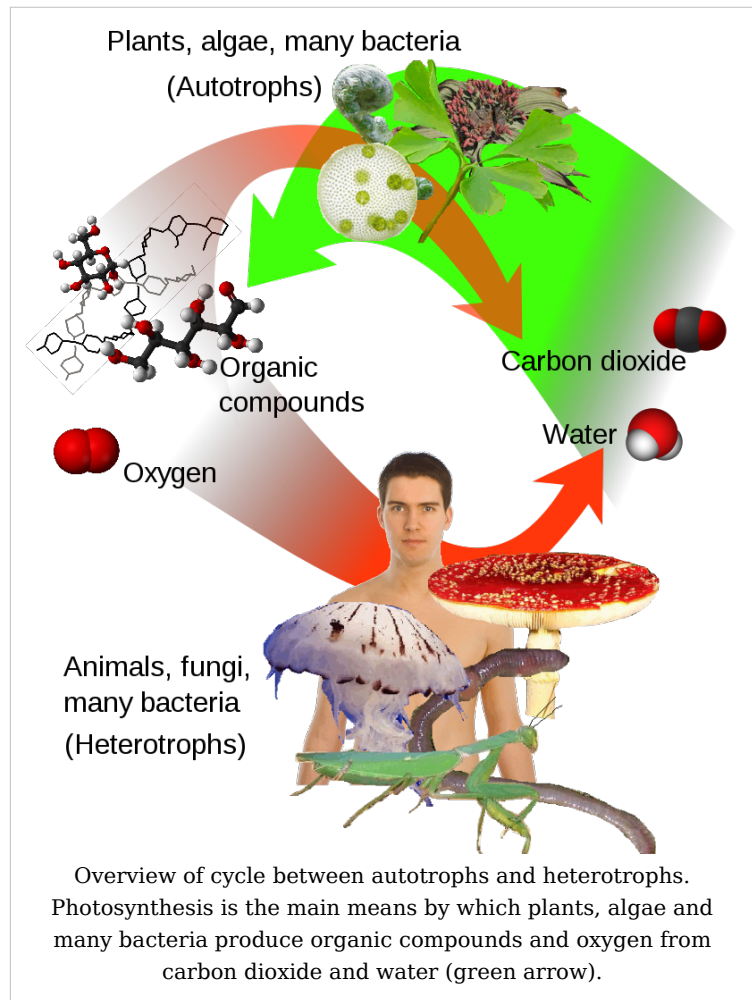
Overview

Photosynthetic organisms are photoautotrophs, which means that they are able to synthesize food directly from carbon dioxide using energy from light. However, not all organisms that use light as a source of energy carry out photosynthesis, since *photoheterotrophs* use organic compounds, rather than carbon dioxide, as a source of carbon [2] . In plants, algae and cyanobacteria, photosynthesis releases oxygen. This is called *oxygenic photosynthesis*. Although there are some differences between oxygenic photosynthesis in plants, algae and cyanobacteria, the overall process is quite similar in these organisms. However, there are some types of bacteria that carry out *anoxygenic photosynthesis*, which consumes carbon dioxide but does not release oxygen.

Photosynthesis splits water to liberate O_2 and fixes CO_2 into sugar
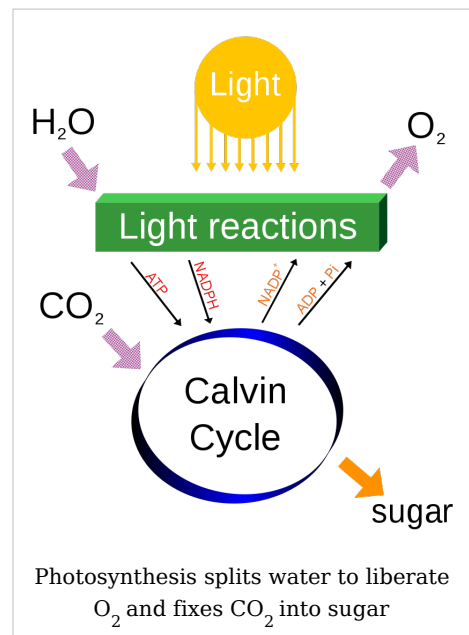
Carbon dioxide is converted into sugars in a process called carbon fixation. Carbon fixation is a redox reaction, so photosynthesis needs to supply both a source of energy to drive this process, and also the electrons needed to convert carbon dioxide into carbohydrate, which is a reduction reaction. In general outline, photosynthesis is the opposite of cellular respiration, where glucose and other compounds are oxidized to produce carbon dioxide, water, and release chemical energy. However, the two processes take place through a different sequence of chemical reactions and in different cellular compartments.

The general equation for photosynthesis is therefore:

CO_2 + 2 H_2A + photons → $(CH_2O)_n$ + O_2 + 2A

carbon dioxide + electron donor + light energy → carbohydrate + oxygen + oxidized electron donor

Since water is most often used as the electron donor in oxygenic photosynthesis, the equation for this process is:

CO_2 + 2 H_2O + photons → $(CH_2O)_n$ + H_2O + O_2
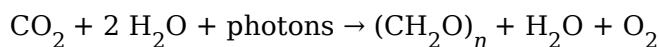
carbon dioxide + water + light energy → carbohydrate + oxygen + water

Other processes (e.g. as used by microbial species in Mono Lake, California) substitute other compounds (such as arsenite) for water in the electron-supply role; the microbes use sunlight to oxidize arsenite to arsenate:[13] The equation for this reaction is:

$(AsO_3{}^{3-})$ + CO_2 + photons → CO + $(AsO_4{}^{3-})$[14]

carbon dioxide + arsenite + light energy → arsenate + carbon monoxide (used to build other compounds in subsequent reactions)

Photosynthesis occurs in two stages. In the first stage, *light-dependent reactions* or *light reactions* capture the energy of light and use it to make the energy-storage molecules ATP and NADPH. During the second stage, the *light-independent reactions* use these products to capture and reduce carbon dioxide.

Photosynthetic membranes and organelles

The proteins that gather light for photosynthesis are embedded within cell membranes. The simplest way these are arranged is in photosynthetic bacteria, where these proteins are held within the plasma membrane.[15] However, this membrane may be tightly-folded into cylindrical sheets called thylakoids,[16] or bunched up into round vesicles called *intracytoplasmic membranes*.[17] These structures can fill most of the interior of a cell, giving the membrane a very large surface area and therefore increasing the amount of light that the bacteria can absorb.[16]
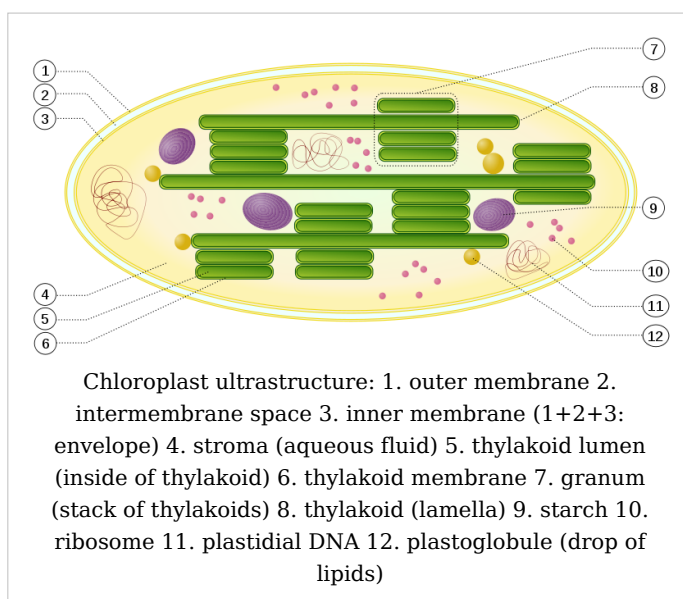
Chloroplast ultrastructure: 1. outer membrane 2. intermembrane space 3. inner membrane (1+2+3: envelope) 4. stroma (aqueous fluid) 5. thylakoid lumen (inside of thylakoid) 6. thylakoid membrane 7. granum (stack of thylakoids) 8. thylakoid (lamella) 9. starch 10. ribosome 11. plastidial DNA 12. plastoglobule (drop of lipids)

In plants and algae, photosynthesis takes place in organelles called chloroplasts. A chloroplast has both an inner and an outer phospholipid membrane. Between these two layers is the intermembrane space. A typical plant cell contains about 10 to 100 chloroplasts. Within the stroma are stacks of thylakoids, the sub-organelles which are the site of photosynthesis. The thylakoids are arranged in stacks called grana (singular: granum). A thylakoid has a flattened disk shape. Inside it is an empty area called the thylakoid space or lumen. The thylakoid membrane contains many integral and peripheral membrane proteins. The proteins complexes which contain special pigments absorbing light energy are called photosystems.

Plants absorb light primarily using the pigment chlorophyll, which is the reason that most plants have a green color. Besides chlorophyll, plants also use pigments such as carotenes and xanthophylls.[18] Algae also use chlorophyll, but various other pigments are present as phycocyanin, carotenes, and xanthophylls in green algae, phycoerythrin in red algae (rhodophytes) and fucoxanthol in brown algae and diatoms resulting in a wide variety of colors.

These pigments are embedded in plants and algae in special antenna-proteins. In such proteins all the pigments are ordered to work well together. Such a protein is also called a light-harvesting complex.

Although all cells in the green parts of a plant have chloroplasts, most of the energy is captured in the leaves. The cells in the interior tissues of a leaf, called the mesophyll, can contain between 450,000 and 800,000 chloroplasts for every square millimeter of leaf. The surface of the leaf is uniformly coated with a water-resistant waxy cuticle that protects the leaf from excessive evaporation of water and decreases the absorption of ultraviolet or blue light to reduce heating. The transparent epidermis layer allows light to pass through to the palisade mesophyll cells where most of the photosynthesis takes place.

Light reactions

In the light reactions, one molecule of the pigment chlorophyll absorbs one photon and loses one electron. This electron is passed to a modified form of chlorophyll called pheophytin, which passes the electron to a quinone molecule, allowing the start of a flow of electrons down an electron transport chain that leads to the ultimate reduction of NADP to NADPH. In addition, this creates a proton gradient across the chloroplast membrane; its dissipation is used by ATP synthase for the

Light-dependent reactions of photosynthesis at the thylakoid membrane

concomitant synthesis of ATP. The chlorophyll molecule regains the lost electron from a water molecule through a process called photolysis, which releases a dioxygen (O_2) molecule. The overall equation for the light-dependent reactions under the conditions of non-cyclic electron flow in green plants is:[19]

$$2 \; H_2O + 2 \; NADP^+ + 2 \; ADP + 2 \; P_i + light \rightarrow 2 \; NADPH + 2 \; H^+ + 2 \; ATP + O_2$$
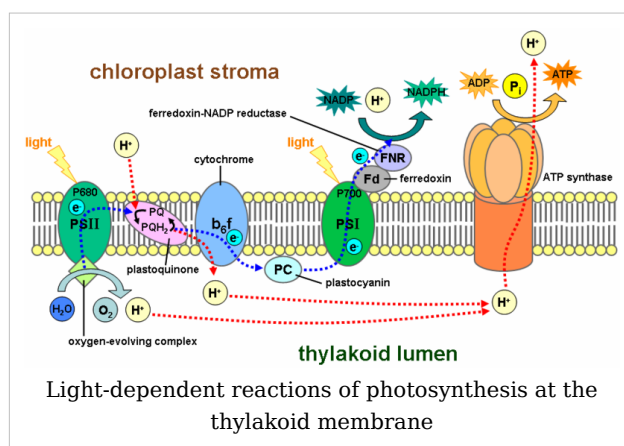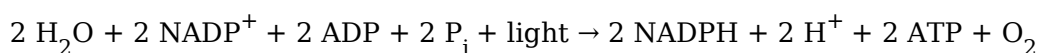
Not all wavelengths of light can support photosynthesis. The photosynthetic action spectrum depends on the type of accessory pigments present. For example, in green plants, the action spectrum resembles the absorption spectrum for chlorophylls and carotenoids with peaks for violet-blue and red light. In red algae, the action spectrum overlaps with the absorption spectrum of phycobilins for blue-green light, which allows these algae to grow in deeper waters that filter out the longer wavelengths used by green plants. The non-absorbed part of the light spectrum is what gives photosynthetic organisms their color (e.g., green plants, red algae, purple bacteria) and is the least effective for photosynthesis in the respective organisms.

Z scheme

In plants, light-dependent reactions occur in the thylakoid membranes of the chloroplasts and use light energy to synthesize ATP and NADPH. The light-dependent reaction has two forms: cyclic and non-cyclic. In the non-cyclic reaction, the photons are captured in the light-harvesting antenna complexes of photosystem II by chlorophyll and other accessory pigments (see diagram at right). When a chlorophyll molecule at the core of the photosystem II reaction center obtains sufficient excitation energy from the adjacent antenna pigments, an electron is transferred to the primary electron-acceptor molecule, Pheophytin, through a process called photoinduced charge separation. These electrons are shuttled through an electron transport chain, the so called *Z-scheme* shown in the diagram, that initially functions to generate a chemiosmotic potential across the

A Photosystem: A **light-harvesting** cluster of photosynthetic pigments present in the thylakoid membrane of chloroplasts.

The "Z scheme"

membrane. An ATP synthase enzyme uses the chemiosmotic potential to make ATP during photophosphorylation, whereas NADPH is a product of the terminal redox reaction in the *Z-scheme*. The electron enters the Photosystem I molecule. The electron is excited due to the light absorbed by the photosystem. A second electron carrier accepts the electron, which again is passed down lowering energies of electron acceptors. The energy created by the electron acceptors is used to move hydrogen ions across the thylakoid membrane into the lumen. The electron is used to reduce the co-enzyme NADP, which has functions in the light-independent reaction. The cyclic reaction is similar to that of the non-cyclic, but differs in the form that it generates only ATP, and no reduced NADP (NADPH) is created. The cyclic reaction takes place only at photosystem I. Once the electron is displaced from the photosystem, the electron is passed down the electron acceptor molecules and returns back to photosystem I, from where it was emitted, hence the name *cyclic reaction*.
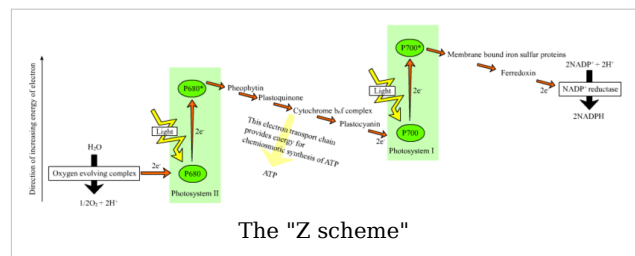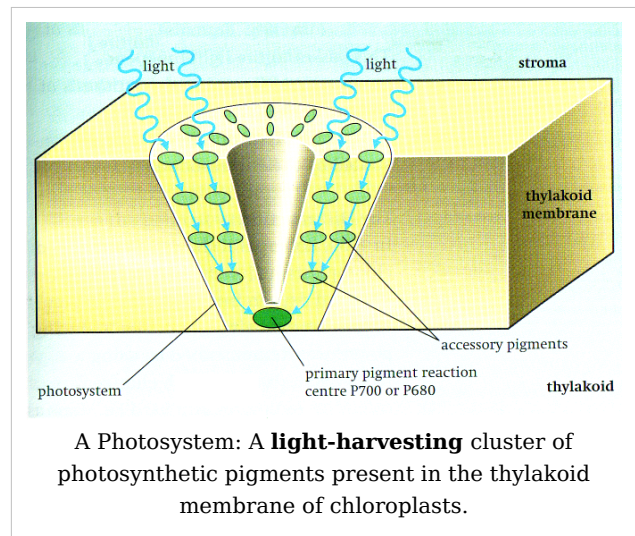
Water photolysis

The NADPH is the main reducing agent in chloroplasts, providing a source of energetic electrons to other reactions. Its production leaves chlorophyll with a deficit of electrons (oxidized), which must be obtained from some other reducing agent. The excited electrons lost from chlorophyll in photosystem I are replaced from the electron transport chain by plastocyanin. However, since photosystem II includes the first steps of the *Z-scheme*, an external source of electrons is required to reduce its oxidized **chlorophyll *a*** molecules. The source of electrons in green-plant and cyanobacterial photosynthesis is water. Two water molecules are oxidized by four successive charge-separation reactions by photosystem II to yield a molecule of diatomic oxygen and four hydrogen ions; the electron yielded in each step is transferred to a redox-active tyrosine residue that then reduces the photoxidized paired-chlorophyll *a* species called P680 that serves as the primary (light-driven) electron donor in the photosystem II reaction center. The oxidation of water is catalyzed in photosystem II by a redox-active structure that contains four manganese ions and a calcium ion; this oxygen-evolving complex binds two water molecules and stores the four oxidizing equivalents that are required to drive the water-oxidizing reaction. Photosystem II is the only known biological enzyme that carries out this oxidation of water. The hydrogen ions contribute to the transmembrane chemiosmotic potential that leads to ATP synthesis. Oxygen is a waste product of light-dependent reactions, but the majority of organisms on Earth use oxygen for cellular respiration, including photosynthetic organisms.[20] [21]

Oxygen and photosynthesis

Light-independent reactions

The Calvin Cycle

In the Light-independent or dark reactions the enzyme RuBisCO captures CO_2 from the atmosphere and in a process that requires the newly formed NADPH, called the Calvin-Benson Cycle, releases three-carbon sugars, which are later combined to form sucrose and starch. The overall equation for the light-independent reactions in green plants is:[19]

$$3\ CO_2 + 9\ ATP + 6\ NADPH + 6\ H^+ \rightarrow C_3H_6O_3\text{-phosphate} + 9\ ADP + 8\ P_i + 6\ NADP^+ + 3\ H_2O$$
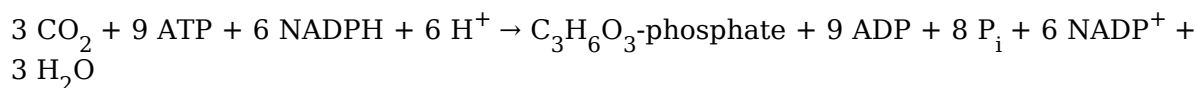
To be more specific, carbon fixation produces an intermediate product, which is then converted to the final carbohydrate products. The carbon skeletons produced by photosynthesis are then variously used to form other organic compounds, such as the building material cellulose, as precursors for lipid and amino acid biosynthesis, or as a fuel in cellular respiration. The latter occurs not only in plants but also in animals when the energy from plants gets passed through a food chain.

The fixation or reduction of carbon dioxide is a process in which carbon dioxide

Overview of the Calvin cycle and carbon fixation

combines with a five-carbon sugar, ribulose 1,5-bisphosphate (RuBP), to yield two molecules of a three-carbon compound, glycerate 3-phosphate (GP), also known as 3-phosphoglycerate (PGA). GP, in the presence of ATP and NADPH from the light-dependent stages, is reduced to glyceraldehyde 3-phosphate (G3P). This product is also referred to as 3-phosphoglyceraldehyde (PGAL) or even as triose phosphate. Triose is a 3-carbon sugar (see carbohydrates). Most (5 out of 6 molecules) of the G3P produced is used to regenerate RuBP so the process can continue (see Calvin-Benson cycle). The 1 out of 6 molecules of the triose phosphates not "recycled" often condense to form hexose phosphates, which ultimately yield sucrose, starch and cellulose. The sugars produced during carbon metabolism yield carbon skeletons that can be used for other metabolic reactions like the production of amino acids and lipids.
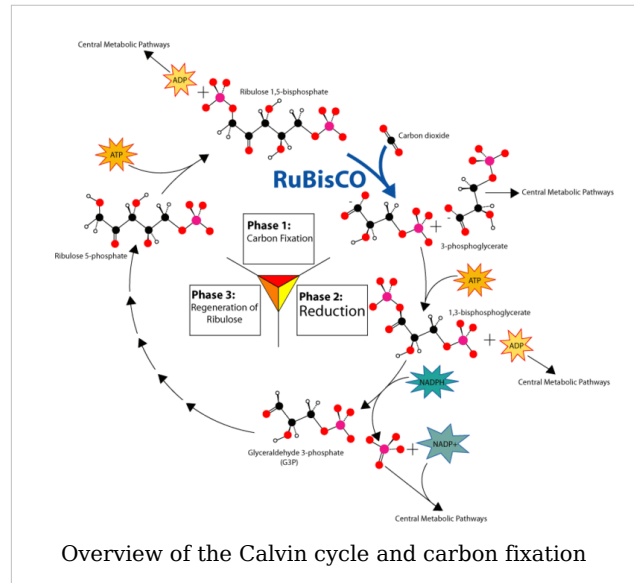
C$_4$ and C$_3$ photosynthesis and CAM

In hot and dry conditions, plants will close their stomata to prevent loss of water. Under these conditions, CO_2 will decrease, and dioxygen gas, produced by the light reactions of photosynthesis, will increase in the leaves, causing an increase of photorespiration by the oxygenase activity of ribulose-1,5-bisphosphate carboxylase/oxygenase and decrease in carbon fixation. Some plants have evolved mechanisms to increase the CO_2 concentration in the leaves under these conditions.

C_4 *plants* chemically fix carbon dioxide in the cells of the mesophyll by adding it to

Overview of C4 carbon fixation
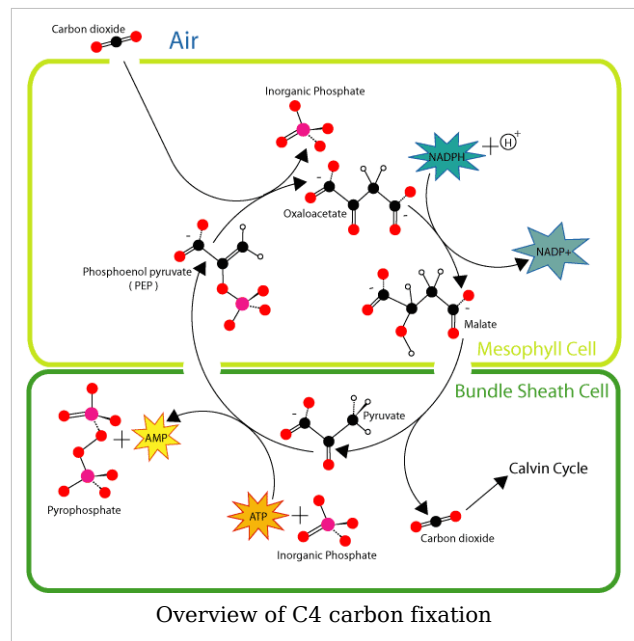
the three-carbon molecule phosphoenolpyruvate (PEP), a reaction catalyzed by an enzyme called PEP carboxylase and which creates the four-carbon organic acid, oxaloacetic acid. Oxaloacetic acid or malate synthesized by this process is then translocated to specialized bundle sheath cells where the enzyme, rubisco, and other Calvin cyle enzymes are located, and where CO_2 released by decarboxylation of the four-carbon acids is then fixed by rubisco activity to the three-carbon sugar 3-Phosphoglyceric acids. The physical separation of rubisco from the oxygen-generating light reactions reduces photorespiration and increases CO_2 fixation and thus photosynthetic capacity of the leaf. [22] C_4 plants can produce more sugar than C_3 plants in conditions of high light and temperature. Many important crop plants are C_4 plants including maize, sorghum, sugarcane, and millet. Plants lacking PEP-carboxylase are called *C_3 plants* because the primary carboxylation reaction, catalyzed by rubisco, produces the three-carbon sugar 3-phosphoglyceric acids directly in the Calvin-Benson Cycle.

Xerophytes such as cacti and most succulents also use PEP carboxylase to capture carbon dioxide in a process called Crassulacean acid metabolism (CAM). In contrast to C4 metabolism, which *physically* separates the CO_2 fixation to PEP from the Calvin cycle, CAM only *temporally* separates these two processes. CAM plants have a different leaf anatomy than C_4 plants, and fix the CO_2 at night, when their stomata are open. CAM plants store the CO_2 mostly in the form of malic acid via carboxylation of phosphoenolpyruvate to oxaloacetate, which is then reduced to malate. Decarboxylation of malate during the day releases CO_2 inside the leaves thus allowing carbon fixation to 3-phosphoglycerate by rubisco.

Order and kinetics

The overall process of photosynthesis takes place in four stages. The first, energy transfer in antenna chlorophyll takes place in the femtosecond [1 femtosecond (fs) = $10,^{-15}$ s] to picosecond [1 picosecond (ps) = 10^{-12} s] time scale. The next phase, the transfer of electrons in photochemical reactions, takes place in the picosecond to nanosecond time scale [1 nanosecond (ns) = 10^{-9} s]. The third phase, the electron transport chain and ATP synthesis, takes place on the microsecond [1 microsecond (μs) = 10^{-6} s] to millisecond [1 millisecond (ms) = 10^{-3} s) time scale. The final phase is carbon fixation and export of stable products and takes place in the millisecond to second time scale. The first three stages occur in the thylakoid membranes.

Efficiency

Plants usually convert light into chemical energy with a photosynthetic efficiency of 3-6%.[23] Actual plants' photosynthetic efficiency varies with the frequency of the light being converted, light intensity, temperature and proportion of CO_2 in the atmosphere, and can vary from 0.1% to 8%.[24] By comparison, solar panels convert light into electric energy at a photosynthetic efficiency of approximately 6-20% for mass-produced panels, and up to 41% in a research laboratory.[25]

Evolution

Early photosynthetic systems, such as those from green and purple sulfur and green and purple non-sulfur bacteria, are thought to have been anoxygenic, using various molecules as electron donors. Green and purple sulfur bacteria are thought to have used hydrogen and sulfur as an electron donor. Green nonsulfur bacteria used various amino and other organic acids. Purple nonsulfur bacteria used a variety of non-specific organic molecules. The use of these molecules is consistent with the geological evidence that the atmosphere was highly reduced at that time.
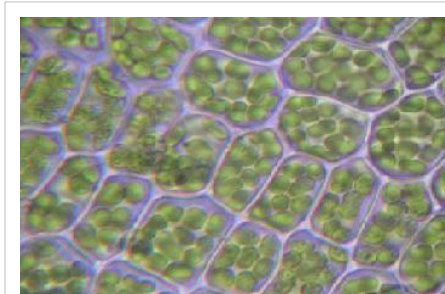
Plant cells with visible chloroplasts.

Fossils of what are thought to be filamentous photosynthetic organisms have been dated at 3.4 billion years old.[26]

The main source of oxygen in the atmosphere is oxygenic photosynthesis, and its first appearance is sometimes referred to as the oxygen catastrophe. Geological evidence suggests that oxygenic photosynthesis, such as that in cyanobacteria, became important during the Paleoproterozoic era around 2 billion years ago. Modern photosynthesis in plants and most photosynthetic prokaryotes is oxygenic. Oxygenic photosynthesis uses water as an electron donor which is oxidized to molecular dioxygen (O_2) in the photosynthetic reaction center.

Symbiosis and the origin of chloroplasts

Several groups of animals have formed symbiotic relationships with photosynthetic algae. These are most common in corals, sponges and sea anemones, possibly due to these animals having particularly simple body plans and large surface areas compared to their volumes.[27] In addition, a few marine molluscs *Elysia viridis* and *Elysia chlorotica* also maintain a symbiotic relationship with chloroplasts that they capture from the algae in their diet and then store in their bodies. This allows the molluscs to survive solely by photosynthesis for several months at a time.[28] [29] Some of the genes from the plant cell nucleus have even been transferred to the slugs, so that the chloroplasts can be supplied with proteins that they need to survive.[30]

An even closer form of symbiosis may explain the origin of chloroplasts. Chloroplasts have many similarities with photosynthetic bacteria including a circular chromosome, prokaryotic-type ribosomes, and similar proteins in the photosynthetic reaction center.[31] [32] The endosymbiotic theory suggests that photosynthetic bacteria were acquired (by endocytosis) by early eukaryotic cells to form the first plant cells. Therefore, chloroplasts may be photosynthetic bacteria that adapted to life inside plant cells. Like mitochondria, chloroplasts still possess their own DNA, separate from the nuclear DNA of their plant host cells and the genes in this chloroplast DNA resemble those in cyanobacteria.[33] DNA in chloroplasts codes for redox proteins such as photosynthetic reaction centers. The CoRR Hypothesis proposes that this **Co**-location is required for **R**edox **R**egulation.

Cyanobacteria and the evolution of photosynthesis

The biochemical capacity to use water as the source for electrons in photosynthesis evolved once, in a common ancestor of extant cyanobacteria. The geological record indicates that this transforming event took place early in Earth's history, at least 2450-2320 million years ago (Ma), and possibly much earlier.[34] Available evidence from geobiological studies of Archean (>2500 Ma) sedimentary rocks indicates that life existed 3500 Ma, but the question of when oxygenic photosynthesis evolved is still unanswered. A clear paleontological window on cyanobacterial evolution opened about 2000 Ma, revealing an already-diverse biota of blue-greens. Cyanobacteria remained principal primary producers throughout the Proterozoic Eon (2500-543 Ma), in part because the redox structure of the oceans favored photoautotrophs capable of nitrogen fixation. Green algae joined blue-greens as major primary producers on continental shelves near the end of the Proterozoic, but only with the Mesozoic (251-65 Ma) radiations of dinoflagellates, coccolithophorids, and diatoms did primary production in marine shelf waters take modern form. Cyanobacteria remain critical to marine ecosystems as primary producers in oceanic gyres, as agents of biological nitrogen fixation, and, in modified form, as the plastids of marine algae.[35]

Discovery

Although some of the steps in photosynthesis are still not completely understood, the overall photosynthetic equation has been known since the 1800s.

Jan van Helmont began the research of the process in the mid-1600s when he carefully measured the mass of the soil used by a plant and the mass of the plant as it grew. After noticing that the soil mass changed very little, he hypothesized that the mass of the growing plant must come from the water, the only substance he added to the potted plant. His hypothesis was partially accurate—much of the gained mass also comes from carbon dioxide as well as water. However, this was a signaling point to the idea that the bulk of a plant's biomass comes from the inputs of photosynthesis, not the soil itself.

Joseph Priestley, a chemist and minister, discovered that when he isolated a volume of air under an inverted jar, and burned a candle in it, the candle would burn out very quickly, much before it ran out of wax. He further discovered that a mouse could similarly "injure" air. He then showed that the air that had been "injured" by the candle and the mouse could be restored by a plant.

In 1778, Jan Ingenhousz, court physician to the Austrian Empress, repeated Priestley's experiments. He discovered that it was the influence of sunlight on the plant that could cause it to rescue a mouse in a matter of hours.

In 1796, Jean Senebier, a Swiss pastor, botanist, and naturalist, demonstrated that green plants consume carbon dioxide and release oxygen under the influence of light. Soon afterwards, Nicolas-Théodore de Saussure showed that the increase in mass of the plant as it grows could not be due only to uptake of CO_2, but also to the incorporation of water. Thus the basic reaction by which photosynthesis is used to produce food (such as glucose) was outlined.

Cornelis Van Niel made key discoveries explaining the chemistry of photosynthesis. By studying purple sulfur bacteria and green bacteria he was the first scientist to demonstrate that photosynthesis is a light-dependent redox reaction, in which hydrogen reduces carbon

dioxide.

Robert Emerson discovered two light reactions by testing plant productivity using different wavelengths of light. With the red alone, the light reactions were suppressed. When blue and red were combined, the output was much more substantial. Thus, there were two photosystems, one aborbing up to 600 nm wavelengths, the other up to 700. The former is known as PSII, the latter is PSI. PSI contains only chlorophyll a, PSII contains primarily chlorophyll a with most of the available chlorophyll b, among other pigments.[36]

Further experiments to prove that the oxygen developed during the photosynthesis of green plants came from water, were performed by Robert Hill in 1937 and 1939. He showed that isolated chloroplasts give off oxygen in the presence of unnatural reducing agents like iron oxalate, ferricyanide or benzoquinone after exposure to light. The Hill reaction is as follows:

$$2\ H_2O + 2\ A + (light, chloroplasts) \rightarrow 2\ AH_2 + O_2$$
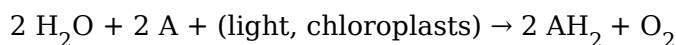
where A is the electron acceptor. Therefore, in light the electron acceptor is reduced and oxygen is evolved. Cyt b_6, now known as a plastoquinone, is one electron acceptor.

Samuel Ruben and Martin Kamen used radioactive isotopes to determine that the oxygen liberated in photosynthesis came from the water.

Melvin Calvin and Andrew Benson, along with James Bassham, elucidated the path of carbon assimilation (the photosynthetic carbon reduction cycle) in plants. The carbon reduction cycle is known as the Calvin cycle, which inappropriately ignores the contribution of Bassham and Benson. Many scientists refer to the cycle as the Calvin-Benson Cycle, Benson-Calvin, and some even call it the Calvin-Benson-Bassham (or CBB) Cycle.

A Nobel Prize winning scientist, Rudolph A. Marcus, was able to discover the function and significance of the electron transport chain.

Factors

There are three main factors affecting photosynthesis and several corollary factors. The three main are:

- Light irradiance and wavelength
- Carbon dioxide concentration
- Temperature.

Light intensity (irradiance), wavelength and temperature

In the early 1900s Frederick Frost Blackman along with Gabrielle Matthaei investigated the effects of light intensity (irradiance) and temperature on the rate of carbon assimilation.

- At constant temperature, the rate of carbon assimilation varies with irradiance, initially increasing as the irradiance increases. However at higher irradiance this relationship no longer holds and the rate of carbon assimilation reaches a plateau.
- At constant irradiance, the rate of carbon assimilation increases as the temperature is increased over a limited range. This effect is only seen at high irradiance levels. At low irradiance, increasing the temperature has little influence on the rate of carbon assimilation.

These two experiments illustrate vital points: firstly, from research it is known that photochemical reactions are not generally affected by temperature. However, these experiments clearly show that temperature affects the rate of carbon assimilation, so there

must be two sets of reactions in the full process of carbon assimilation. These are of course the light-dependent 'photochemical' stage and the light-independent, temperature-dependent stage. Second, Blackman's experiments illustrate the concept of limiting factors. Another limiting factor is the wavelength of light. Cyanobacteria, which reside several meters underwater, cannot receive the correct wavelengths required to cause photoinduced charge separation in conventional photosynthetic pigments. To combat this problem, a series of proteins with different pigments surround the reaction center.This unit is called a phycobilisome.

Carbon dioxide levels and photorespiration

As carbon dioxide concentrations rise, the rate at which sugars are made by the light-independent reactions increases until limited by other factors. RuBisCO, the enzyme that captures carbon dioxide in the light-independent reactions, has a binding affinity for both carbon dioxide and oxygen. When the concentration of carbon dioxide is high, RuBisCO will fix carbon dioxide. However, if the carbon dioxide concentration is low, RuBisCO will bind oxygen instead of carbon dioxide. This process, called photorespiration, uses energy, but does not produce sugars.

RuBisCO oxygenase activity is disadvantageous to plants for several reasons:

1. One product of oxygenase activity is phosphoglycolate (2 carbon) instead of 3-phosphoglycerate (3 carbon). Phosphoglycolate cannot be metabolized by the Calvin-Benson cycle and represents carbon lost from the cycle. A high oxygenase activity, therefore, drains the sugars that are required to recycle ribulose 5-bisphosphate and for the continuation of the Calvin-Benson cycle.
2. Phosphoglycolate is quickly metabolized to glycolate that is toxic to a plant at a high concentration; it inhibits photosynthesis.
3. Salvaging glycolate is an energetically expensive process that uses the glycolate pathway and only 75% of the carbon is returned to the Calvin-Benson cycle as 3-phosphoglycerate. The reactions also produce ammonia (NH_3) which is able to diffuse out of the plant leading to a loss of nitrogen.

A highly-simplified summary is:

$$2 \text{ glycolate} + ATP \rightarrow 3\text{-phosphoglycerate} + \text{carbon dioxide} + ADP + NH_3$$
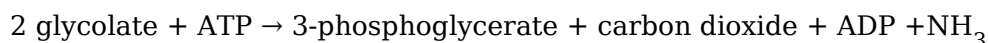
The salvaging pathway for the products of RuBisCO oxygenase activity is more commonly known as photorespiration, since it is characterized by light-dependent oxygen consumption and the release of carbon dioxide.

See also
- Artificial photosynthesis
- Calvin-Benson cycle
- Carbon fixation
- Cellular respiration
- Chemosynthesis
- Light-dependent reaction
- Photobiology
- Photoinhibition
- Photosynthetic reaction center

- Photosynthetically active radiation
- Quantum biology
- Red edge
- Jan Anderson (scientist)

Footnotes

α. ^ The word photosynthesis comes from the Greek *φώτο- (photo-)*, "light," and *σύνθεσις (synthesis)*, "placing with."

β. ^ The exceptions are chemoautotrophs that live in rocks or around deep sea hydrothermal vents.

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External links

- A collection of photosynthesis pages for all levels from a renowned expert (Govindjee) (http://www.life.uiuc.edu/govindjee/linksPSed.htm)
- UC Berkeley video lecture (http://academicearth.org/lectures/photosynthesis--from-light-to-atp) on Photosynthesis
- In depth, advanced treatment of photosynthesis, also from Govindjee (http://www.life.uiuc.edu/govindjee/paper/gov.html)
- Science Aid: Photosynthesis (http://scienceaid.co.uk/biology/biochemistry/photosynthesis.html) Article appropriate for high school science
- Liverpool John Moores University, Dr.David Wilkinson (http://www.ljmu.ac.uk/NewsCentre/63012.htm)
- Metabolism, Cellular Respiration and Photosynthesis - The Virtual Library of Biochemistry and Cell Biology (http://www.biochemweb.org/metabolism.shtml)
- Overall examination of Photosynthesis at an intermediate level (http://www.chemsoc.org/networks/learnnet/cfb/Photosynthesis.htm)
- Overall Energetics of Photosynthesis (http://www.life.uiuc.edu/govindjee/photosynBook.html)
- Photosynthesis Discovery Milestones (http://www.juliantrubin.com/bigten/photosynthesisexperiments.html) - experiments and background

Computational biology

Computational biology is an interdisciplinary field that applies the techniques of computer science, applied mathematics and statistics to address biological problems. The main focus lays on developing mathematical modeling and computational simulation techniques. By these means it addresses scientific reaserch topics with their theoretical and experimental questions without a laboratory. It encompasses the fields of:

- Bioinformatics, which applies algorithms and statistical techniques to the interpretation, classification and understanding of biological datasets. These typically consist of large numbers of DNA, RNA, or protein sequences. Sequence alignment is used to assemble the datasets for analysis. Comparisons of homologous sequences, gene finding, and prediction of gene expression are the most common techniques used on assembled datasets; however, analysis of such datasets have many applications throughout all fields of biology.

- Computational biomodeling, a field within biocybernetics concerned with building computational models of biological systems.

- Computational genomics, a field within genomics which studies the genomes of cells and organisms. High-throughput genome sequencing produces lots of data, which requires extensive post-processing (genome assembly) and uses DNA microarray technologies to perform statistical analyses on the genes expressed in individual cell types. This can help find genes of interests for certain diseases or conditions. This field also studies the mathematical foundations of sequencing.

- Molecular modeling, which consists of modelling the behaviour of molecules of biological importance.

- Protein structure prediction and structural genomics, which attempt to systematically produce accurate structural models for three-dimensional protein structures that have not been determined experimentally.

- Computational biochemistry and biophysics, which make extensive use of structural modeling and simulation methods such as molecular dynamics and Monte Carlo method-inspired Boltzmann sampling methods in an attempt to elucidate the kinetics and thermodynamics of protein functions.

Goldbeter-Koshland kinetics

The **Goldbeter-Koshland kinetics** describe a steady-state solution for a 2-state biological system. In this system, the interconversion between these two states is performed by two enzymes with opposing effect. One example would be a protein Z that exists in a phosphorylated form Z_P and in an unphosphorylated form Z; the corresponding kinase Y and phosphatase X interconvert the two forms. In this case we would be interested in the equilibrium concentration of the protein Z (Goldbeter-Koshland kinetics only describe equilibrium properties, thus no dynamics can be modeled). It has many applications in the description of biological systems.

A kinase Y and a phosphotase X that act on a protein Z; one possible application for the Goldbeter-Koshland kinetics

The Goldbeter-Koshland kinetics is described by the Goldbeter-Koshland function:

$$z = \frac{[Z]}{[Z]_0} = G(v_1, v_2, J_1, J_2) = \frac{2v_1 J_2}{B + \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}$$

with the constants

$$v_1 = k_1[X]; \ v_2 = k_2[Y]; \ J_1 = \frac{K_{M1}}{[Z]_0}; \ J_2 = \frac{K_{M2}}{[Z]_0}; \ B = v_2 - v_1 + J_1 v_2 + J_2 v_1$$

Graphically the function takes values between 0 and 1 and has a sigmoid behavior. The smaller the parameters J_1 and J_2 the steeper the function gets and the more of a *switch-like* behavior is observed.

Derivation

Since we are looking at equilibrium properties we can write

$$\frac{d[Z]}{dt} \overset{!}{=} 0$$

From Michaelis–Menten kinetics we know that the rate at which Z_P is dephosphorylated is $r_1 = \frac{k_1[X][Z_P]}{K_{M1} + [Z_P]}$ and the rate at which Z is phosphorylated is $r_2 = \frac{k_2[Y][Z]}{K_{M2} + [Z]}$. Here the K_M stand for the Michaelis Menten constant which describes how well the enzymes X and Y bind and catalyze the conversion whereas the kinetic parameters k_1 and k_2 denote the rate constants for the catalyzed reactions. Assuming that the total concentration of Z is constant we can additionally write that $[Z]_0 = [Z_P] + [Z]$ and we thus get:

$$\frac{d[Z]}{dt} = r_1 - r_2 = \frac{k_1[X]([Z]_0 - [Z])}{K_{M1} + ([Z]_0 - [Z])} - \frac{k_2[Y][Z]}{K_{M2} + [Z]} = 0$$

$$\frac{k_1[X]([Z]_0 - [Z])}{K_{M1} + ([Z]_0 - [Z])} = \frac{k_2[Y][Z]}{K_{M2} + [Z]}$$

$$\frac{k_1[X](1 - \frac{[Z]}{[Z]_0})}{\frac{K_{M1}}{[Z]_0} + (1 - \frac{[Z]}{[Z]_0})} = \frac{k_2[Y]\frac{[Z]}{[Z]_0}}{\frac{K_{M2}}{[Z]_0} + \frac{[Z]}{[Z]_0}}$$

$$\frac{v_1(1 - z)}{J_1 + (1 - z)} = \frac{v_2 z}{J_2 + z} \qquad (1)$$

with the constants

$$z = \frac{[Z]}{[Z]_0}; \quad v_1 = k_1[X]; \quad v_2 = k_2[Y]; \quad J_1 = \frac{K_{M1}}{[Z]_0}; \quad J_2 = \frac{K_{M2}}{[Z]_0}; \qquad (2)$$

If we thus solve the quadratic equation (1) for z we get:

$$\frac{v_1(1 - z)}{J_1 + (1 - z)} = \frac{v_2 z}{J_2 + z}$$

$$J_2 v_1 + z v_1 - J_2 v_1 z - z^2 v_1 = z v_2 J_1 + v_2 z - z^2 v_2$$

$$z^2(v_2 - v_1) - z \underbrace{(v_2 - v_1 + J_1 v_2 + J_2 v_1)}_{B} + v_1 J_2 = 0$$

$$z = \frac{B - \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}{2(v_2 - v_1)} = \frac{B - \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}{2(v_2 - v_1)} \cdot \frac{B + \sqrt{B^2 - 4(v_2 - v_1)}}{B + \sqrt{B^2 - 4(v_2 - v_1)}}$$

$$z = \frac{4(v_2 - v_1)v_1 J_2}{2(v_2 - v_1)} \cdot \frac{1}{B + \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}$$

$$z = \frac{2v_1 J_2}{B + \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}. \qquad (3)$$

Thus (3) is a solution to the initial equilibrium problem and describes the equilibrium concentration of [Z] and [Z$_p$] as a function of the kinetic parameters of the phoshorylation and dephoshorylation reaction and the concentrations of the kinase and phosphotase. The solution is the Goldbeter-Koshland function with the constants from (2):

$$z = \frac{[Z]}{[Z]_0} = G(v_1, v_2, J_1, J_2) = \frac{2v_1 J_2}{B + \sqrt{B^2 - 4(v_2 - v_1)v_1 J_2}}.$$

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Metabolic network

A **metabolic network** is the complete set of metabolic and physical processes that determine the physiological and biochemical properties of a cell. As such, these networks comprise the chemical reactions of metabolism as well as the regulatory interactions that guide these reactions.

With the sequencing of complete genomes, it is now possible to reconstruct the network of biochemical reactions in many organisms, from bacteria to human. Several of these networks are available online: Kyoto Encyclopedia of Genes and Genomes (KEGG)[1], EcoCyc [2] and BioCyc [3]. Metabolic networks are powerful tools, for studying and modelling metabolism. From the study of metabolic networks' topology with graph theory to predictive toxicology and ADME.

See also

- Metabolic network modelling
- Metabolic pathway

References

[1] http://www.genome.ad.jp
[2] http://www.ecocyc.org
[3] http://biocyc.org

Signalling pathway

1. REDIRECT signal transduction

Cell cycle

The **cell cycle**, or **cell-division cycle**, is the series of events that take place in a cell leading to its division and duplication (replication). In cells without a nucleus (prokaryotes), the cell cycle occurs via a process termed binary fission. In cells with a nucleus (eukaryotes), the cell cycle can be divided in two brief periods: interphase—during which the cell grows, accumulating nutrients needed for mitosis and duplicating its DNA—and the mitosis (M) phase, during which the cell splits itself into two distinct cells, often called "daughter cells". The cell-division cycle is a vital process by which a single-celled fertilized egg develops into a mature organism, as well as the process by which hair, skin, blood cells, and some internal organs are renewed.

Phases

The cell cycle consists of five distinct phases: G_1 phase, S phase (synthesis), G_2 phase (collectively known as interphase) and M phase (mitosis). M phase is itself composed of two tightly coupled processes: mitosis, in which the cell's chromosomes are divided between the two daughter cells, and cytokinesis, in which the cell's cytoplasm divides forming distinct cells. Activation of each phase is dependent on the proper progression and completion of the previous one. Cells that have temporarily or reversibly stopped dividing are said to have entered a state of quiescence called G_0 phase.

Schematic of the cell cycle. outer ring: I=Interphase, M=Mitosis; inner ring: M=Mitosis, G_1=Gap 1, G_2=Gap 2, S=Synthesis; not in ring: G_0=Gap 0/Resting. The duration of mitosis in relation to the other phases has been exaggerated in this diagram.
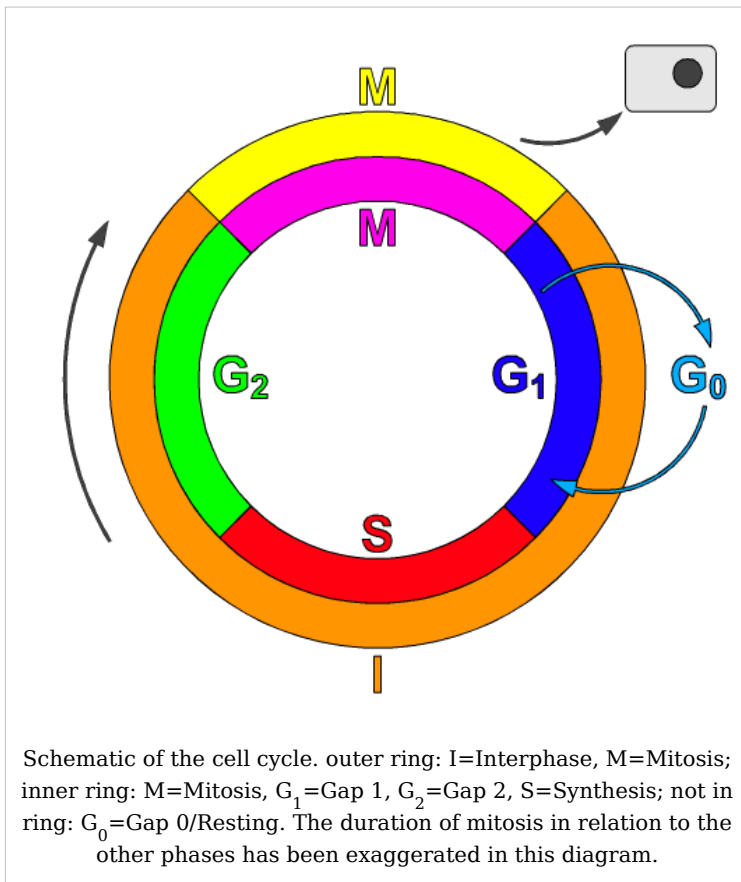
State	Phase	Abbreviation	Description
quiescent/ senescent	Gap 0	G_0	A resting phase where the cell has left the cycle and has stopped dividing.

Interphase	Gap 1	G_1	Cells increase in size in Gap 1. The G_1 *checkpoint* control mechanism ensures that everything is ready for DNA synthesis.
	Synthesis	S	DNA replication occurs during this phase.
	Gap 2	G_2	During the gap between DNA synthesis and mitosis, the cell will continue to grow. The G_2 *checkpoint* control mechanism ensures that everything is ready to enter the M (mitosis) phase and divide.
Cell division	Mitosis	M	Cell growth stops at this stage and cellular energy is focused on the orderly division into two daughter cells. A checkpoint in the middle of mitosis (*Metaphase Checkpoint*) ensures that the cell is ready to complete cell division.

After cell division, each of the daughter cells begin the interphase of a new cycle. Although the various stages of interphase are not usually morphologically distinguishable, each phase of the cell cycle has a distinct set of specialized biochemical processes that prepare the cell for initiation of cell division.

Resting (G_0 phase)

The term "post-mitotic" is sometimes used to refer to both quiescent and senescent cells. Nonproliferative cells in multicellular eukaryotes generally enter the quiescent G_0 state from G_1 and may remain quiescent for long periods of time, possibly indefinitely (as is often the case for neurons). This is very common for cells that are fully differentiated. Cellular senescence is a state that occurs in response to DNA damage or degradation that would make a cell's progeny nonviable; it is often a biochemical alternative to the self-destruction of such a damaged cell by apoptosis.

Interphase

G_1 phase

The first phase within interphase, from the end of the previous M phase until the beginning of DNA synthesis is called G_1 (G indicating *gap*). During this phase the biosynthetic activities of the cell, which had been considerably slowed down during M phase, resume at a high rate. This phase is marked by synthesis of various enzymes that are required in S phase, mainly those needed for DNA replication. Duration of G_1 is highly variable, even among different cells of the same species.[1]

S phase

The ensuing S phase starts when DNA synthesis commences; when it is complete, all of the chromosomes have been replicated, i.e., each chromosome has two (sister) chromatids. Thus, during this phase, the amount of DNA in the cell has effectively doubled, though the ploidy of the cell remains the same. Rates of RNA transcription and protein synthesis are very low during this phase. An exception to this is histone production, most of which occurs during the S phase.[2] [3] [4]

G$_2$ phase

The cell then enters the G$_2$ phase, which lasts until the cell enters mitosis. Again, significant protein synthesis occurs during this phase, mainly involving the production of microtubules, which are required during the process of mitosis. Inhibition of protein synthesis during G$_2$ phase prevents the cell from undergoing mitosis.

Mitosis (M Phase)

The relatively brief M phase consists of nuclear division (karyokinesis) and cytoplasmic division (cytokinesis). In plants and algae, cytokinesis is accompanied by the formation of a new cell wall. The M phase has been broken down into several distinct phases, sequentially known as prophase, Prometaphase, metaphase, anaphase and telophase leading to cytokinesis.

Regulation of eukaryotic cell cycle

Regulation of the cell cycle involves processes crucial to the survival of a cell, including the detection and repair of genetic damage as well as the prevention of uncontrolled cell division. The molecular events that control the cell cycle are ordered and directional; that is, each process occurs in a sequential fashion and it is impossible to "reverse" the cycle.

Role of cyclins and CDKs

Two key classes of regulatory molecules, cyclins and cyclin-dependent kinases (CDKs), determine a cell's progress through the cell cycle.[5] Leland H. Hartwell, R. Timothy Hunt, and Paul M. Nurse won the 2001 Nobel Prize in Physiology or Medicine for their discovery of these central molecules.[6] Many of the genes encoding cyclins and CDKs are conserved among all eukaryotes, but in general more complex organisms have more elaborate cell cycle control systems

Regulation of cell cycle: Schematic

that incorporate more individual components. Many of the relevant genes were first identified by studying yeast, especially *Saccharomyces cerevisiae*;[7] genetic nomenclature in yeast dubs many these genes *cdc* (for "cell division cycle") followed by an identifying number, e.g., *cdc25*.

Cyclins form the regulatory subunits and CDKs the catalytic subunits of an activated heterodimer; cyclins have no catalytic activity and CDKs are inactive in the absence of a partner cyclin. When activated by a bound cyclin, CDKs perform a common biochemical
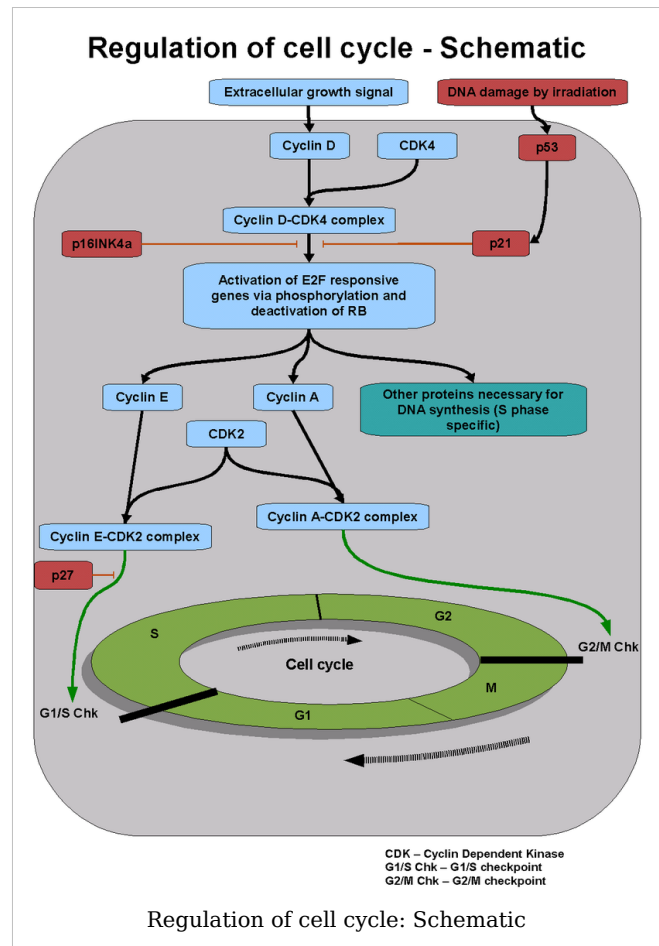
reaction called phosphorylation that activates or inactivates target proteins to orchestrate coordinated entry into the next phase of the cell cycle. Different cyclin-CDK combinations determine the downstream proteins targeted. CDKs are constitutively expressed in cells whereas cyclins are synthesised at specific stages of the cell cycle, in response to various molecular signals.[8]

General mechanism of cyclin-CDK interaction

Upon receiving a pro-mitotic extracellular signal, G_1 cyclin-CDK complexes become active to prepare the cell for S phase, promoting the expression of transcription factors that in turn promote the expression of S cyclins and of enzymes required for DNA replication. The G_1 cyclin-CDK complexes also promote the degradation of molecules that function as S phase inhibitors by targeting them for ubiquitination. Once a protein has been ubiquitinated, it is targeted for proteolytic degradation by the proteasome. Active S cyclin-CDK complexes phosphorylate proteins that make up the pre-replication complexes assembled during G_1 phase on DNA replication origins. The phosphorylation serves two purposes: to activate each already-assembled pre-replication complex, and to prevent new complexes from forming. This ensures that every portion of the cell's genome will be replicated once and only once. The reason for prevention of gaps in replication is fairly clear, because daughter cells that are missing all or part of crucial genes will die. However, for reasons related to gene copy number effects, possession of extra copies of certain genes would also prove deleterious to the daughter cells.

Mitotic cyclin-CDK complexes, which are synthesized but inactivated during S and G_2 phases, promote the initiation of mitosis by stimulating downstream proteins involved in chromosome condensation and mitotic spindle assembly. A critical complex activated during this process is a ubiquitin ligase known as the anaphase-promoting complex (APC), which promotes degradation of structural proteins associated with the chromosomal kinetochore. APC also targets the mitotic cyclins for degradation, ensuring that telophase and cytokinesis can proceed. Interphase: Interphase generally lasts at least 12 to 24 hours in mammalian tissue. During this period, the cell is constantly synthesizing RNA, producing protein and growing in size. By studying molecular events in cells, scientists have determined that interphase can be divided into 4 steps: Gap 0 (G0), Gap 1 (G1), S (synthesis) phase, Gap 2 (G2).

Specific action of cyclin-CDK complexes

Cyclin D is the first cyclin produced in the cell cycle, in response to extracellular signals (eg. growth factors). Cyclin D binds to existing CDK4, forming the active cyclin D-CDK4 complex. Cyclin D-CDK4 complex in turn phosphorylates the retinoblastoma susceptibility protein (Rb). The hyperphosphorylated Rb dissociates from the E2F/DP1/Rb complex (which was bound to the E2F responsive genes, effectively "blocking" them from transcription), activating E2F. Activation of E2F results in transcription of various genes like cyclin E, cyclin A, DNA polymerase, thymidine kinase, etc. Cyclin E thus produced binds to CDK2, forming the cyclin E-CDK2 complex, which pushes the cell from G_1 to S phase (G_1/S transition). Cyclin B along with cdc2 (cdc2 - fission yeasts (CDK1 - mammalia)) forms the cyclin B-cdc2 complex, which initiates the G_2/M transition.[9] Cyclin B-cdc2 complex activation causes breakdown of nuclear envelope and initiation of prophase, and subsequently, its deactivation causes the cell to exit mitosis.[8]

Inhibitors

Two families of genes, the *cip/kip* family and the INK4a/ARF (*In*hibitor of *K*inase 4/*A*lternative *R*eading *F*rame) prevent the progression of the cell cycle. Because these genes are instrumental in prevention of tumor formation, they are known as tumor suppressors.

The ***cip/kip* family** includes the genes p21, p27 and p57. They halt cell cycle in G_1 phase, by binding to, and inactivating, cyclin-CDK complexes. p21 is activated by p53 (which, in turn, is triggered by DNA damage eg. due to radiation). p27 is activated by Transforming Growth Factor β (TGF β), a growth inhibitor.

The **INK4a/ARF family** includes p16INK4a, which binds to CDK4 and arrests the cell cycle in G_1 phase, and p14arf which prevents p53 degradation. And the amount of chromosomes are able to double at the same rate as in phase 2.

Checkpoints

Cell cycle checkpoints are used by the cell to monitor and regulate the progress of the cell cycle.[10] Checkpoints prevent cell cycle progression at specific points, allowing verification of necessary phase processes and repair of DNA damage. The cell cannot proceed to the next phase until checkpoint requirements have been met.

Several checkpoints are designed to ensure that damaged or incomplete DNA is not passed on to daughter cells. Two main checkpoints exist: the G1/S checkpoint and the G2/M checkpoint. G1/S transition is a rate-limiting step in the cell cycle and is also known as restriction point.[8] An alternative model of the cell cycle response to DNA damage has also been proposed, known as the postreplication checkpoint.

p53 plays an important role in triggering the control mechanisms at both G1/S and G2/M checkpoints.

Role in tumor formation

A disregulation of the cell cycle components may lead to tumor formation. As mentioned above, some genes like the cell cycle inhibitors, RB, p53 etc., when they mutate, may cause the cell to multiply uncontrollably, forming a tumor. Although the duration of cell cycle in tumor cells is equal to or longer than that of normal cell cycle, the proportion of cells that are in active cell division (versus quiescent cells in G0 phase) in tumors is much higher than that in normal tissue. Thus there is a net increase in cell number as the number of cells that die by apoptosis or senescence remains the same.

The cells which are actively undergoing cell cycle are targeted in cancer therapy as the DNA is relatively exposed during cell division and hence susceptible to damage by drugs or radiation. This fact is made use of in cancer treatment; by a process known as debulking, a significant mass of the tumor is removed which pushes a significant number of the remaining tumor cells from G0 to G1 phase (due to increased availability of nutrients, oxygen, growth factors etc.). Radiation or chemotherapy following the debulking procedure kills these cells which have newly entered the cell cycle. [8]

Synchronization of cell cultures

Several methods can be used to synchronise cell cultures by halting the cell cycle at a particular phase. For example, Serum starvation[11] and treatment with Thymidine or Aphidicolin[12] halt the cell in the G1 phase, Mitotic shake-off, treatment with colchicine[13] and treatment with Nocodazole[14] halt the cell in M phase and treatment with 5-fluorodeoxyuridine halts the cell in S phase.

See also

- cell cycle mathematical model
- Mitosis
- Meiosis
- Interphase

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- Cell cycle and metabolic cycle regulated transcription in yeast (http://www.sceptrans.org)
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- KEGG - Human Cell Cycle (http://www.genome.ad.jp/kegg/pathway/hsa/hsa04110.html)
- Cell cycle modeling (http://mpf.biol.vt.edu/Research.html)

DNA

Deoxyribonucleic acid (**DNA**) is a nucleic acid that contains the genetic instructions used in the development and functioning of all known living organisms and some viruses. The main role of DNA molecules is the long-term storage of information. DNA is often compared to a set of blueprints or a recipe, or a code, since it contains the instructions needed to construct other components of cells, such as proteins and RNA molecules. The DNA segments that carry this genetic information are called genes, but other DNA sequences have structural purposes, or are involved in regulating the use of this genetic information.

Chemically, DNA consists of two long polymers of simple units called nucleotides, with backbones made of sugars and phosphate groups joined by ester bonds. These two strands run in opposite directions to each other and are therefore anti-parallel. Attached to each sugar is one of four types of molecules called bases. It is the sequence of these four bases along the backbone that encodes information. This information is read using the genetic code, which specifies the sequence of the

The structure of part of a DNA double helix

amino acids within proteins. The code is read by copying stretches of DNA into the related nucleic acid RNA, in a process called transcription.

Within cells, DNA is organized into X-shaped structures called chromosomes. These chromosomes are duplicated before cells divide, in a process called DNA replication. Eukaryotic organisms (animals, plants, fungi, and protists) store most of their DNA inside the cell nucleus and some of their DNA in the mitochondria (animals and plants) and chloroplasts (plants only)[1] . Prokaryotes (bacteria and archaea) however, store their DNA in the cell's cytoplasm. Within the chromosomes, chromatin proteins such as histones compact and organize DNA. These compact structures guide the interactions between DNA and other proteins, helping control which parts of the DNA are transcribed.

Properties

Strands of purified DNA precipitated from solutions of cell components are visible as viscous white substance.

DNA is a long polymer made from repeating units called nucleotides.[2] [3] [4] These nucleotides are adenine (A), guanine (G), cytosine (C) and thymine (T). In the related nucleic acid RNA, thymine is replaced by uracil (U). These nucleotides can be classified into two groups: purines (adenine and guanine) and pyrimidines (thymine and cytosine).

The DNA chain is 22 to 26 Ångströms wide (2.2 to 2.6 nanometres), and one nucleotide unit is 3.3 Å (0.33 nm) long.[5] Although each individual repeating unit is very small, DNA polymers can be very large molecules containing millions of nucleotides. For instance, the largest human chromosome, chromosome number 1, is approximately 220 million base pairs long.[6]

In living organisms, DNA does not usually exist as a single molecule, but instead as a pair of molecules that are held tightly together.[7] [8] These two long strands entwine like vines, in the shape of a double helix. The nucleotide repeats contain both the segment of the backbone of the molecule, which holds the chain together, and a base, which interacts with the other DNA strand in the helix. In general, a base linked to a sugar is called a nucleoside and a base linked to a sugar and one or more phosphate groups is called a nucleotide. If multiple nucleotides are linked together, as in DNA, this polymer is called a polynucleotide.[9]

The backbone of the DNA strand is made from alternating phosphate and sugar residues.[10] The sugar in DNA is 2-deoxyribose, which is a pentose (five-carbon) sugar. The sugars are joined together by phosphate groups that form phosphodiester bonds between

The chemical structure of DNA. Hydrogen bonds are shown as dotted lines.
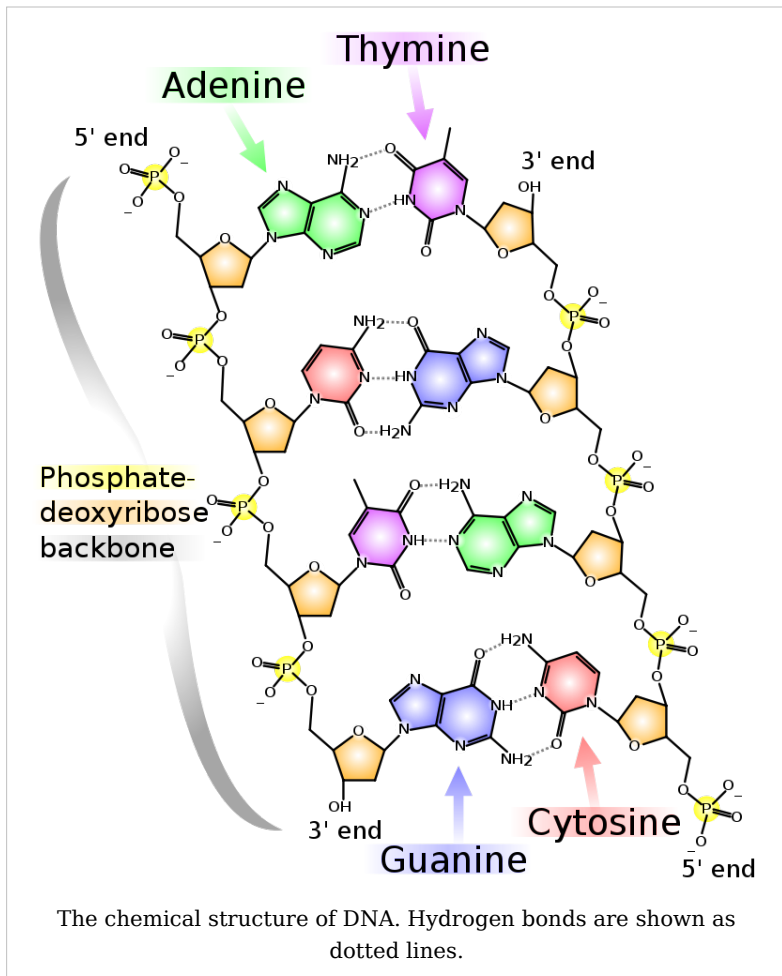
the third and fifth carbon atoms of adjacent sugar rings. These asymmetric bonds mean a strand of DNA has a direction. In a double helix the direction of the nucleotides in one strand is opposite to their direction in the other strand. This arrangement of DNA strands is called antiparallel. The asymmetric ends of DNA strands are referred to as the 5□ (*five prime*) and 3□ (*three prime*) ends, with the 5' end being that with a terminal phosphate group and the 3' end that with a terminal hydroxyl group. One of the major differences between DNA and RNA is the sugar, with 2-deoxyribose being replaced by the alternative pentose sugar ribose in RNA.[8]

The DNA double helix is stabilized by hydrogen bonds between the bases attached to the two strands. The four bases found in DNA are adenine (abbreviated A), cytosine (C), guanine (G) and thymine (T). These four bases are attached to the sugar/phosphate to form the complete nucleotide, as shown for adenosine monophosphate.

These bases are classified into two types; adenine and guanine are fused five- and six-membered heterocyclic compounds called purines, while cytosine and thymine are six-membered rings called pyrimidines.[8] A fifth pyrimidine base, called uracil (U), usually takes the place of thymine in RNA and differs from thymine by lacking a methyl group on its ring. Uracil is not usually found in DNA, occurring only as a breakdown product of cytosine.

Grooves

Twin helical strands form the DNA backbone. Another double helix may be found by tracing the spaces, or grooves, between the strands. These voids are adjacent to the base pairs and may provide a binding site. As the strands are not directly opposite each other, the grooves are unequally sized. One groove, the major groove, is 22 Å wide and the other, the minor groove, is 12 Å wide.[12] The narrowness of the minor groove means that the edges of the bases are more accessible in the major groove. As a result, proteins like transcription factors that can bind to specific sequences in double-stranded DNA usually make contacts to the sides of the bases exposed in the major groove.[13] This situation varies in unusual conformations of DNA within the cell *(see below)*, but the major and minor grooves are always named to reflect the differences in size that would be seen if the DNA is twisted back into the ordinary B form.

Structure of a section of DNA. The bases lie horizontally between the two spiraling strands.[11] Animated version at File:DNA orbit animated.gif - over 3 megabytes.

Base pairing

Each type of base on one strand forms a bond with just one type of base on the other strand. This is called complementary base pairing. Here, purines form hydrogen bonds to pyrimidines, with A bonding only to T, and C bonding only to G. This arrangement of two nucleotides binding together across the double helix is called a base pair. As hydrogen bonds are not covalent, they can be broken and rejoined relatively easily.

The two strands of DNA in a double helix can therefore be pulled apart like a zipper, either by a mechanical force or high temperature.[14] As a result of this complementarity, all the information in the double-stranded sequence of a DNA helix is duplicated on each strand, which is vital in DNA replication. Indeed, this reversible and specific interaction between complementary base pairs is critical for all the functions of DNA in living organisms.[3]
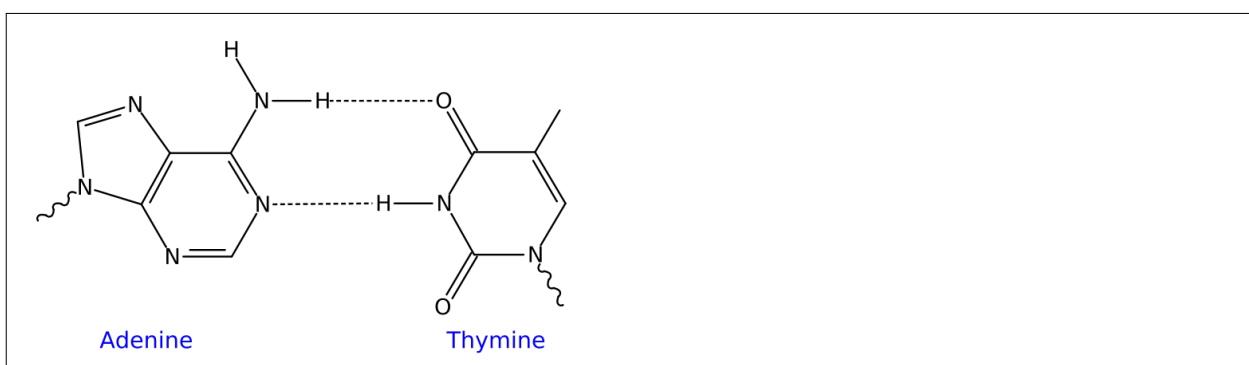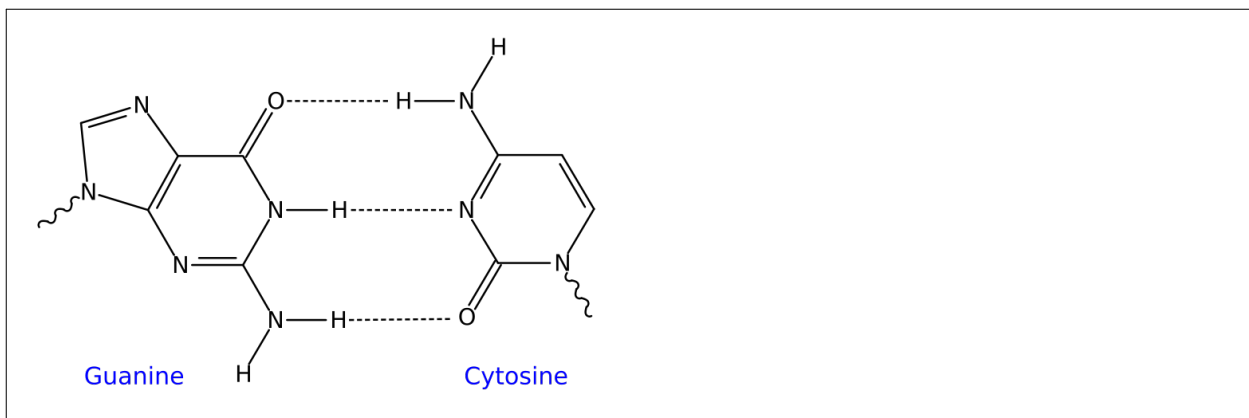
Top, a **GC** base pair with three hydrogen bonds. Bottom, an **AT** base pair with two hydrogen bonds. Non-covalent hydrogen bonds between the pairs are shown as dashed lines.

The two types of base pairs form different numbers of hydrogen bonds, AT forming two hydrogen bonds, and GC forming three hydrogen bonds (see figures, left). DNA with high GC-content is more stable than DNA with low GC-content, but contrary to popular belief, this is not due to the extra hydrogen bond of a GC basepair but rather the contribution of stacking interactions (hydrogen bonding merely provides specificity of the pairing, not stability).[15] As a result, it is both the percentage of GC base pairs and the overall length of a DNA double helix that determine the strength of the association between the two strands of DNA. Long DNA helices with a high GC content have stronger-interacting strands, while short helices with high AT content have weaker-interacting strands.[16] In biology, parts of the DNA double helix that need to separate easily, such as the TATAAT Pribnow box in some promoters, tend to have a high AT content, making the strands easier to pull apart.[17] In the laboratory, the strength of this interaction can be measured by finding the temperature required to break the hydrogen bonds, their melting temperature (also called T_m value). When all the base pairs in a DNA double helix melt, the strands separate and exist in solution as two entirely independent molecules. These single-stranded DNA molecules have no single common shape, but some conformations are more stable than others.[18]

Sense and antisense

A DNA sequence is called "sense" if its sequence is the same as that of a messenger RNA copy that is translated into protein.[19] The sequence on the opposite strand is called the "antisense" sequence. Both sense and antisense sequences can exist on different parts of the same strand of DNA (i.e. both strands contain both sense and antisense sequences). In both prokaryotes and eukaryotes, antisense RNA sequences are produced, but the functions of these RNAs are not entirely clear.[20] One proposal is that antisense RNAs are involved in regulating gene expression through RNA-RNA base pairing.[21]

A few DNA sequences in prokaryotes and eukaryotes, and more in plasmids and viruses, blur the distinction between sense and antisense strands by having overlapping genes.[22] In these cases, some DNA sequences do double duty, encoding one protein when read along one strand, and a second protein when read in the opposite direction along the other strand. In bacteria, this overlap may be involved in the regulation of gene transcription,[23] while in viruses, overlapping genes increase the amount of information that can be encoded within the small viral genome.[24]

Supercoiling

DNA can be twisted like a rope in a process called DNA supercoiling. With DNA in its "relaxed" state, a strand usually circles the axis of the double helix once every 10.4 base pairs, but if the DNA is twisted the strands become more tightly or more loosely wound.[25] If the DNA is twisted in the direction of the helix, this is positive supercoiling, and the bases are held more tightly together. If they are twisted in the opposite direction, this is negative supercoiling, and the bases come apart more easily. In nature, most DNA has slight negative supercoiling that is introduced by enzymes called topoisomerases.[26] These enzymes are also needed to relieve the twisting stresses introduced into DNA strands during processes such as transcription and DNA replication.[27]

Alternate DNA structures

DNA exists in many possible conformations that include A-DNA, B-DNA, and Z-DNA forms, although, only B-DNA and Z-DNA have been directly observed in functional organisms.[10] The conformation that DNA adopts depends on the hydration level, DNA sequence, the amount and direction of supercoiling, chemical modifications of the bases, the type and concentration of metal ions, as well as the presence of polyamines in solution.[28]

From left to right, the structures of A, B and Z DNA
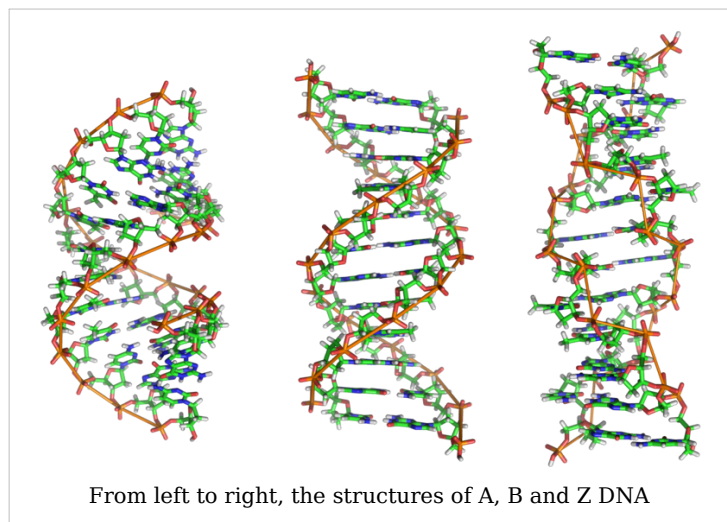
The first published reports of A-DNA X-ray diffraction patterns— and also B-DNA used analyses based on Patterson transforms that provided only a limited amount of structural information for oriented fibers of DNA.[29] [30] An alternate analysis was then proposed by Wilkins *et al.*, in 1953, for the *in vivo* B-DNA X-ray diffraction/scattering patterns of highly

hydrated DNA fibers in terms of squares of Bessel functions.[31] In the same journal, Watson and Crick presented their molecular modeling analysis of the DNA X-ray diffraction patterns to suggest that the structure was a double-helix.[7]

Although the `B-DNA form' is most common under the conditions found in cells,[32] it is not a well-defined conformation but a family of related DNA conformations[33] that occur at the high hydration levels present in living cells. Their corresponding X-ray diffraction and scattering patterns are characteristic of molecular paracrystals with a significant degree of disorder.[34] [35]

Compared to B-DNA, the A-DNA form is a wider right-handed spiral, with a shallow, wide minor groove and a narrower, deeper major groove. The A form occurs under non-physiological conditions in partially dehydrated samples of DNA, while in the cell it may be produced in hybrid pairings of DNA and RNA strands, as well as in enzyme-DNA complexes.[36] [37] Segments of DNA where the bases have been chemically modified by methylation may undergo a larger change in conformation and adopt the Z form. Here, the strands turn about the helical axis in a left-handed spiral, the opposite of the more common B form.[38] These unusual structures can be recognized by specific Z-DNA binding proteins and may be involved in the regulation of transcription.[39]

Quadruplex structures

Structure of a DNA quadruplex formed by telomere repeats. The looped conformation of the DNA backbone is very different from the typical helical structure.[40]
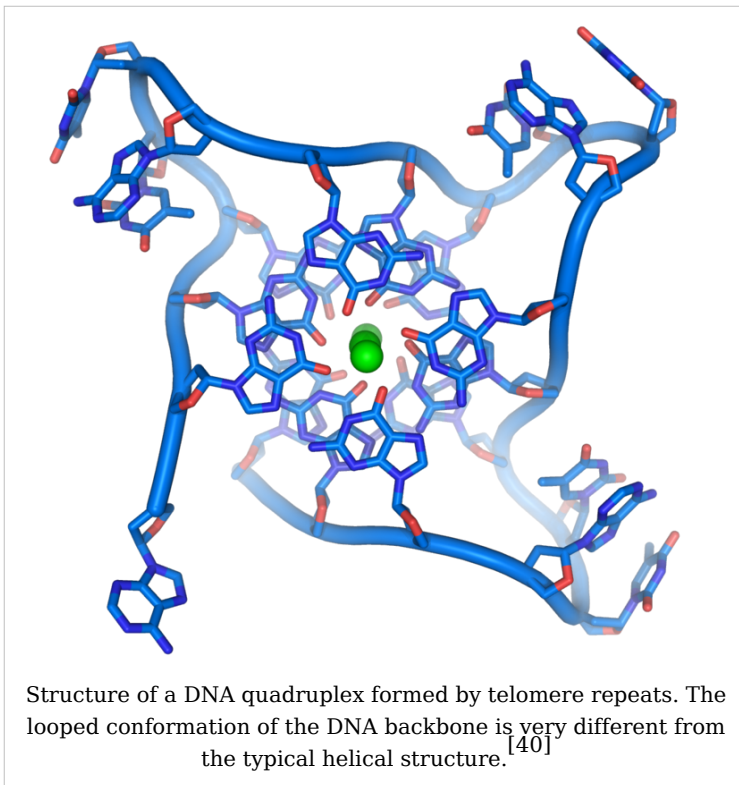
At the ends of the linear chromosomes are specialized regions of DNA called telomeres. The main function of these regions is to allow the cell to replicate chromosome ends using the enzyme telomerase, as the enzymes that normally replicate DNA cannot copy the extreme 3□ ends of chromosomes.[41] These specialized chromosome caps also help protect the DNA ends, and stop the DNA repair systems in the cell from treating them as damage to be corrected.[42] In human cells, telomeres are usually lengths of single-stranded DNA containing several thousand repeats of a simple TTAGGG sequence.[43]

These guanine-rich sequences may stabilize chromosome ends by forming structures of stacked sets of four-base units, rather than the usual base pairs found in other DNA molecules. Here, four guanine bases form a flat plate and these flat four-base units then stack on top of each other, to form a stable *G-quadruplex* structure.[44] These structures are stabilized by hydrogen bonding between the edges of the bases and chelation of a metal ion in the centre of each four-base unit.[45]

Other structures can also be formed, with the central set of four bases coming from either a single strand folded around the bases, or several different parallel strands, each contributing one base to the central structure.
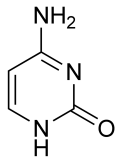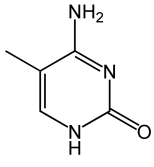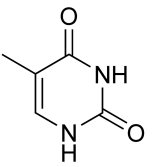
In addition to these stacked structures, telomeres also form large loop structures called telomere loops, or T-loops. Here, the single-stranded DNA curls around in a long circle stabilized by telomere-binding proteins.[46] At the very end of the T-loop, the single-stranded telomere DNA is held onto a region of double-stranded DNA by the telomere strand disrupting the double-helical DNA and base pairing to one of the two strands. This triple-stranded structure is called a displacement loop or D-loop.[44]

Branched DNA

A DNA structure with a single branching point.

A DNA structure with multiple branches.
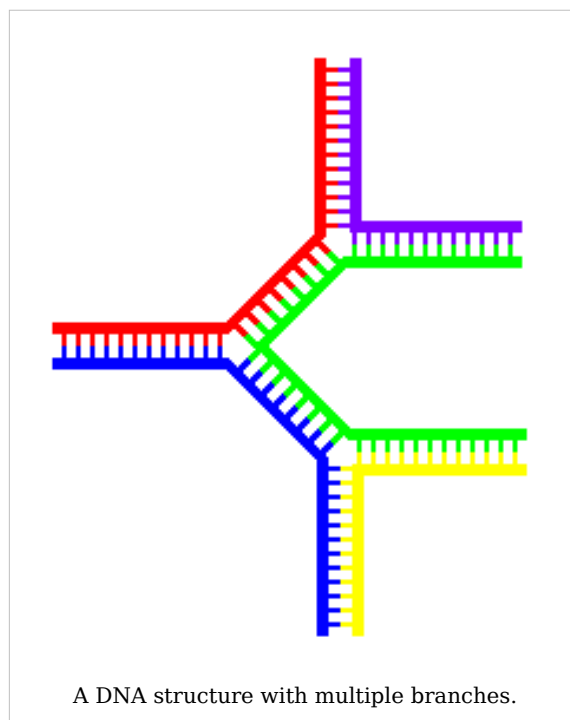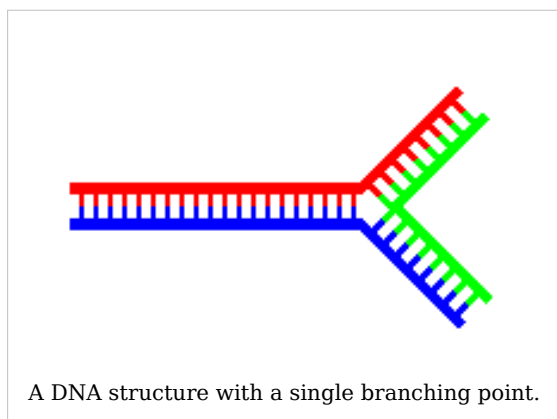
In DNA fraying occurs when non-complementary regions exist at the end of an otherwise complementary double-strand of DNA. However, branched DNA can occur if a third strand of DNA is introduced and contains adjoining regions able to hybridize with the frayed regions of the pre-existing double-strand. Although the simplest example of branched DNA involves only three strands of DNA, complexes involving additional strands and multiple branches are also possible.[47]

Chemical modifications

cytosine	5-methylcytosine	thymine

Structure of cytosine with and without the 5-methyl group. After deamination the 5-methylcytosine has the same structure as thymine

Base modifications

The expression of genes is influenced by how the DNA is packaged in chromosomes, in a structure called chromatin. Base modifications can be involved in packaging, with regions that have low or no gene expression usually containing high levels of methylation of cytosine bases. For example, cytosine methylation, produces 5-methylcytosine, which is important for X-chromosome inactivation.[48] The average level of methylation varies between organisms - the worm *Caenorhabditis elegans* lacks cytosine methylation, while vertebrates have higher levels, with up to 1% of their DNA containing 5-methylcytosine.[49] Despite the importance of 5-methylcytosine, it can deaminate to leave a thymine base, methylated cytosines are therefore particularly prone to mutations.[50] Other base modifications include adenine methylation in bacteria, the presence of 5-hydroxymethylcytosine in the brain,[51] and the glycosylation of uracil to produce the "J-base" in kinetoplastids.[52] [53]

Damage

DNA can be damaged by many different sorts of mutagens, which change the DNA sequence. Mutagens include oxidizing agents, alkylating agents and also high-energy electromagnetic radiation such as ultraviolet light and X-rays. The type of DNA damage produced depends on the type of mutagen. For example, UV light can damage DNA by producing thymine dimers, which are cross-links between pyrimidine bases.[55] On the other hand, oxidants such as free radicals or hydrogen peroxide produce multiple forms of damage, including base modifications, particularly of guanosine, and double-strand breaks.[56] A typical human cell contains about 150,000 bases that have suffered oxidative damage.[57] Of these oxidative lesions, the most dangerous are double-strand breaks, as these are difficult to repair and can produce point mutations, insertions and deletions from the DNA sequence, as well as chromosomal translocations.[58]
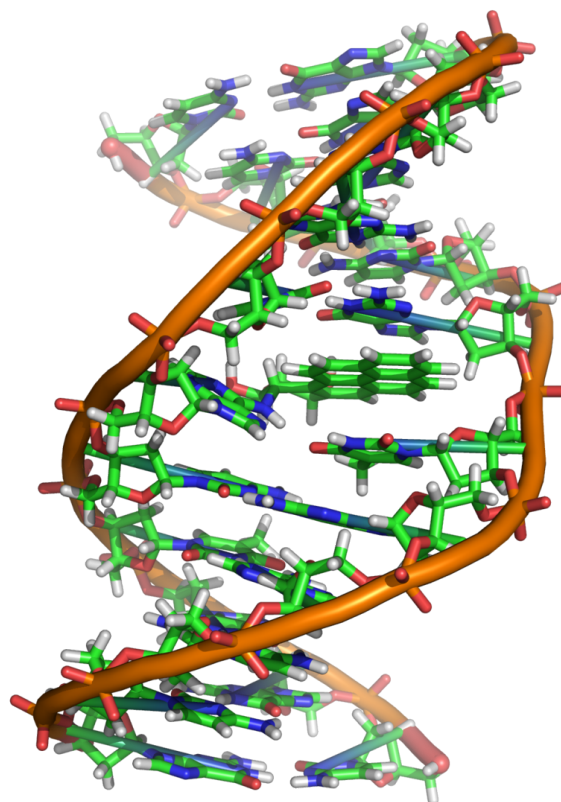
A covalent adduct between benzo[*a*]pyrene, the major mutagen in tobacco smoke, and DNA[54]

Many mutagens fit into the space between two adjacent base pairs, this is called *intercalating*. Most intercalators are aromatic and planar molecules, and include Ethidium bromide, daunomycin, and doxorubicin. In order for an intercalator to fit between base

pairs, the bases must separate, distorting the DNA strands by unwinding of the double helix. This inhibits both transcription and DNA replication, causing toxicity and mutations. As a result, DNA intercalators are often carcinogens, and Benzo[*a*]pyrene diol epoxide, acridines, aflatoxin and ethidium bromide are well-known examples.[59] [60] [61] Nevertheless, due to their ability to inhibit DNA transcription and replication, other similar toxins are also used in chemotherapy to inhibit rapidly growing cancer cells.[62]

Biological functions

DNA usually occurs as linear chromosomes in eukaryotes, and circular chromosomes in prokaryotes. The set of chromosomes in a cell makes up its genome; the human genome has approximately 3 billion base pairs of DNA arranged into 46 chromosomes.[63] The information carried by DNA is held in the sequence of pieces of DNA called genes. Transmission of genetic information in genes is achieved via complementary base pairing. For example, in transcription, when a cell uses the information in a gene, the DNA sequence is copied into a complementary RNA sequence through the attraction between the DNA and the correct RNA nucleotides. Usually, this RNA copy is then used to make a matching protein sequence in a process called translation which depends on the same interaction between RNA nucleotides. Alternatively, a cell may simply copy its genetic information in a process called DNA replication. The details of these functions are covered in other articles; here we focus on the interactions between DNA and other molecules that mediate the function of the genome.

Genes and genomes

Genomic DNA is located in the cell nucleus of eukaryotes, as well as small amounts in mitochondria and chloroplasts. In prokaryotes, the DNA is held within an irregularly shaped body in the cytoplasm called the nucleoid.[64] The genetic information in a genome is held within genes, and the complete set of this information in an organism is called its genotype. A gene is a unit of heredity and is a region of DNA that influences a particular characteristic in an organism. Genes contain an open reading frame that can be transcribed, as well as regulatory sequences such as promoters and enhancers, which control the transcription of the open reading frame.

In many species, only a small fraction of the total sequence of the genome encodes protein. For example, only about 1.5% of the human genome consists of protein-coding exons, with over 50% of human DNA consisting of non-coding repetitive sequences.[65] The reasons for the presence of so much non-coding DNA in eukaryotic genomes and the extraordinary differences in genome size, or *C-value*, among species represent a long-standing puzzle known as the "C-value enigma."[66] However, DNA sequences that do not code protein may still encode functional non-coding RNA molecules, which are involved in the regulation of gene expression.[67]

T7 RNA polymerase (blue) producing a mRNA (green) from a DNA template (orange).[68]
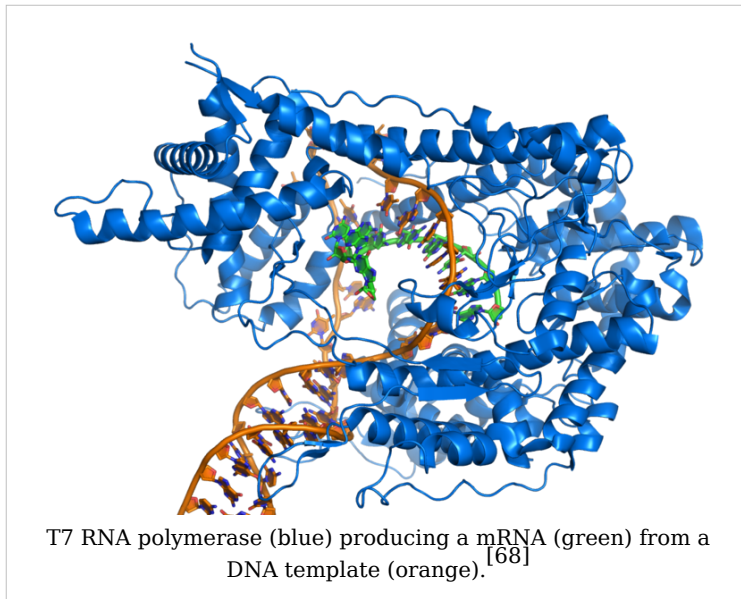
Some non-coding DNA sequences play structural roles in chromosomes. Telomeres and centromeres typically contain few genes, but are important for the function and stability of chromosomes.[42] [69] An abundant form of non-coding DNA in humans are pseudogenes, which are copies of genes that have been disabled by mutation.[70] These sequences are usually just molecular fossils, although they can occasionally serve as raw genetic material for the creation of new genes through the process of gene duplication and divergence.[71]

Transcription and translation

A gene is a sequence of DNA that contains genetic information and can influence the phenotype of an organism. Within a gene, the sequence of bases along a DNA strand defines a messenger RNA sequence, which then defines one or more protein sequences. The relationship between the nucleotide sequences of genes and the amino-acid sequences of proteins is determined by the rules of translation, known collectively as the genetic code. The genetic code consists of three-letter 'words' called *codons* formed from a sequence of three nucleotides (e.g. ACT, CAG, TTT).

In transcription, the codons of a gene are copied into messenger RNA by RNA polymerase. This RNA copy is then decoded by a ribosome that reads the RNA sequence by base-pairing the messenger RNA to transfer RNA, which carries amino acids. Since there are 4 bases in 3-letter combinations, there are 64 possible codons (4^3 combinations). These encode the twenty standard amino acids, giving most amino acids more than one possible codon. There are also three 'stop' or 'nonsense' codons signifying the end of the coding region; these are the TAA, TGA and TAG codons.

Replication

Cell division is essential for an organism to grow, but when a cell divides it must replicate the DNA in its genome so that the two daughter cells have the same genetic information as their parent. The double-stranded structure of DNA provides a simple mechanism for DNA replication. Here, the two strands are separated and then each strand's complementary DNA sequence

DNA replication. The double helix is unwound by a helicase and topoisomerase. Next, one DNA polymerase produces the leading strand copy. Another DNA polymerase binds to the lagging strand. This enzyme makes discontinuous segments (called Okazaki fragments) before DNA ligase joins them together.

is recreated by an enzyme called DNA polymerase. This enzyme makes the complementary strand by finding the correct base through complementary base pairing, and bonding it onto the original strand. As DNA polymerases can only extend a DNA strand in a 5′ to 3′ direction, different mechanisms are used to copy the antiparallel strands of the double helix.[72] In this way, the base on the old strand dictates which base appears on the new strand, and the cell ends up with a perfect copy of its DNA.
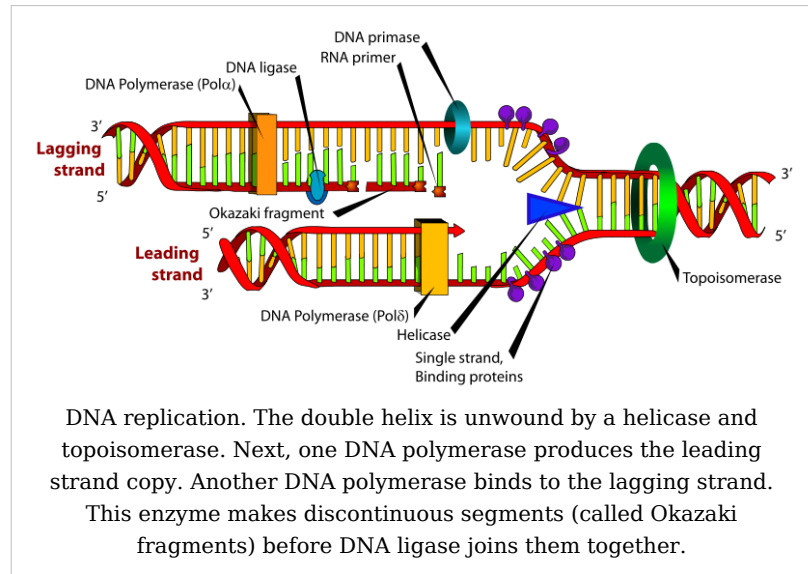
Interactions with proteins

All the functions of DNA depend on interactions with proteins. These protein interactions can be non-specific, or the protein can bind specifically to a single DNA sequence. Enzymes can also bind to DNA and of these, the polymerases that copy the DNA base sequence in transcription and DNA replication are particularly important.

DNA-binding proteins
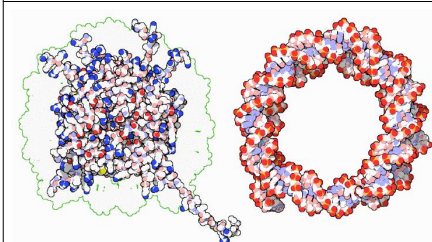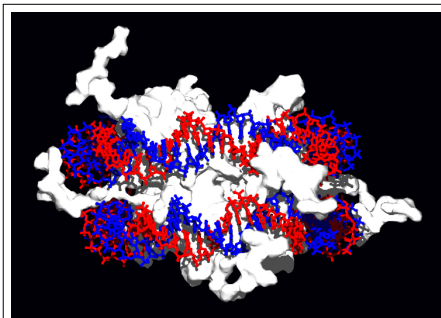
Interaction of DNA with histones (shown in white, top). These proteins' basic amino acids (below left, blue) bind to the acidic phosphate groups on DNA (below right, red).

Structural proteins that bind DNA are well-understood examples of non-specific DNA-protein interactions. Within chromosomes, DNA is held in complexes with structural proteins. These proteins organize the DNA into a compact structure called chromatin. In eukaryotes this structure involves DNA binding to a complex of small basic proteins called histones, while in prokaryotes multiple types of proteins are involved.[73] [74] The histones form a disk-shaped complex called a nucleosome, which contains two complete turns of double-stranded DNA wrapped around its surface. These non-specific interactions are formed through basic residues in the histones making ionic bonds to the acidic sugar-phosphate backbone of the DNA, and are therefore largely independent of the base sequence.[75] Chemical modifications of these basic amino acid residues include methylation, phosphorylation and acetylation.[76] These chemical changes alter the strength of the interaction between the DNA and the histones, making the DNA more or less accessible to transcription factors and changing the rate of transcription.[77] Other non-specific DNA-binding proteins in chromatin include the high-mobility group proteins, which bind to bent or distorted DNA.[78] These proteins are important in bending arrays of nucleosomes and arranging them into the larger structures that make up chromosomes.[79]

A distinct group of DNA-binding proteins are the DNA-binding proteins that specifically bind single-stranded DNA. In humans, replication protein A is the best-understood member of this family and is used in processes where the double helix is separated, including DNA replication, recombination and DNA repair.[80] These binding proteins seem to stabilize single-stranded DNA and protect it from forming stem-loops or being degraded by nucleases.

In contrast, other proteins have evolved to bind to particular DNA sequences. The most intensively studied of these are the various transcription factors, which are proteins that regulate transcription. Each transcription factor binds to one particular set of DNA sequences and activates or inhibits the transcription of genes that have these sequences close to their promoters. The transcription factors do this in two ways. Firstly, they can bind the RNA polymerase responsible for transcription, either directly or through other mediator proteins; this locates the polymerase at the promoter and allows it to begin transcription.[82] Alternatively, transcription factors can bind enzymes that modify the histones at the promoter; this will change the accessibility of the DNA template to the polymerase.[83]

As these DNA targets can occur throughout an organism's genome, changes in the activity of one type of transcription factor can affect thousands of genes.[84] Consequently, these proteins are often the

The lambda repressor helix-turn-helix transcription factor bound to its DNA target[81]
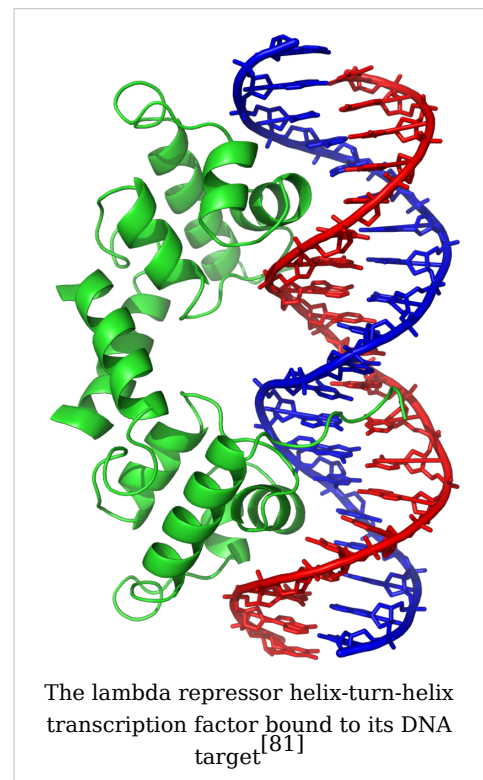
targets of the signal transduction processes that control responses to environmental changes or cellular differentiation and development. The specificity of these transcription

factors' interactions with DNA come from the proteins making multiple contacts to the edges of the DNA bases, allowing them to "read" the DNA sequence. Most of these base-interactions are made in the major groove, where the bases are most accessible.[85]
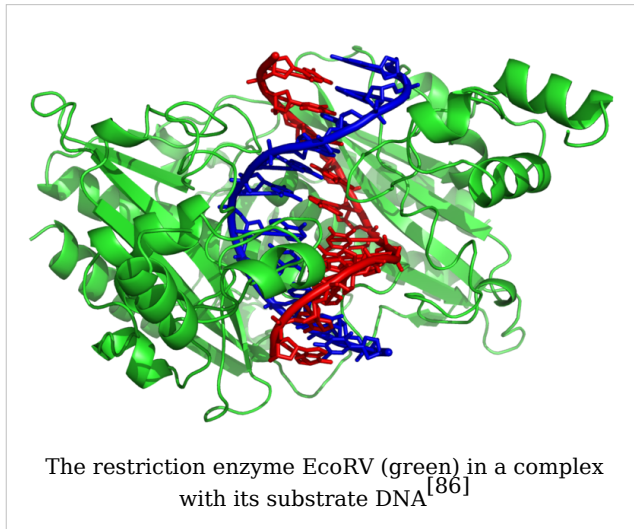
DNA-modifying enzymes

Nucleases and ligases

The restriction enzyme EcoRV (green) in a complex with its substrate DNA[86]

Nucleases are enzymes that cut DNA strands by catalyzing the hydrolysis of the phosphodiester bonds. Nucleases that hydrolyse nucleotides from the ends of DNA strands are called exonucleases, while endonucleases cut within strands. The most frequently used nucleases in molecular biology are the restriction endonucleases, which cut DNA at specific sequences. For instance, the EcoRV enzyme shown to the left recognizes the 6-base sequence 5′-GAT|ATC-3′ and makes a cut at the vertical line. In nature, these enzymes protect bacteria against phage infection by digesting the phage DNA when it enters the bacterial cell, acting as part of the restriction modification system.[87] In technology, these sequence-specific nucleases are used in molecular cloning and DNA fingerprinting.

Enzymes called DNA ligases can rejoin cut or broken DNA strands.[88] Ligases are particularly important in lagging strand DNA replication, as they join together the short segments of DNA produced at the replication fork into a complete copy of the DNA template. They are also used in DNA repair and genetic recombination.[88]

Topoisomerases and helicases

Topoisomerases are enzymes with both nuclease and ligase activity. These proteins change the amount of supercoiling in DNA. Some of these enzyme work by cutting the DNA helix and allowing one section to rotate, thereby reducing its level of supercoiling; the enzyme then seals the DNA break.[26] Other types of these enzymes are capable of cutting one DNA helix and then passing a second strand of DNA through this break, before rejoining the helix.[89] Topoisomerases are required for many processes involving DNA, such as DNA replication and transcription.[27]

Helicases are proteins that are a type of molecular motor. They use the chemical energy in nucleoside triphosphates, predominantly ATP, to break hydrogen bonds between bases and unwind the DNA double helix into single strands.[90] These enzymes are essential for most processes where enzymes need to access the DNA bases.

Polymerases

Polymerases are enzymes that synthesize polynucleotide chains from nucleoside triphosphates. The sequence of their products are copies of existing polynucleotide chains - which are called *templates*. These enzymes function by adding nucleotides onto the 3′ hydroxyl group of the previous nucleotide in a DNA strand. Consequently, all polymerases work in a 5′ to 3′ direction.[91] In the active site of these enzymes, the incoming nucleoside triphosphate base-pairs to the template: this allows polymerases to accurately synthesize the complementary strand of their template. Polymerases are classified according to the type of template that they use.

In DNA replication, a DNA-dependent DNA polymerase makes a copy of a DNA sequence. Accuracy is vital in this process, so many of these polymerases have a proofreading activity. Here, the polymerase recognizes the occasional mistakes in the synthesis reaction by the lack of base pairing between the mismatched nucleotides. If a mismatch is detected, a 3′ to 5′ exonuclease activity is activated and the incorrect base removed.[92] In most organisms DNA polymerases function in a large complex called the replisome that contains multiple accessory subunits, such as the DNA clamp or helicases.[93]

RNA-dependent DNA polymerases are a specialized class of polymerases that copy the sequence of an RNA strand into DNA. They include reverse transcriptase, which is a viral enzyme involved in the infection of cells by retroviruses, and telomerase, which is required for the replication of telomeres.[41] [94] Telomerase is an unusual polymerase because it contains its own RNA template as part of its structure.[42]

Transcription is carried out by a DNA-dependent RNA polymerase that copies the sequence of a DNA strand into RNA. To begin transcribing a gene, the RNA polymerase binds to a sequence of DNA called a promoter and separates the DNA strands. It then copies the gene sequence into a messenger RNA transcript until it reaches a region of DNA called the terminator, where it halts and detaches from the DNA. As with human DNA-dependent DNA polymerases, RNA polymerase II, the enzyme that transcribes most of the genes in the human genome, operates as part of a large protein complex with multiple regulatory and accessory subunits.[95]

Genetic recombination
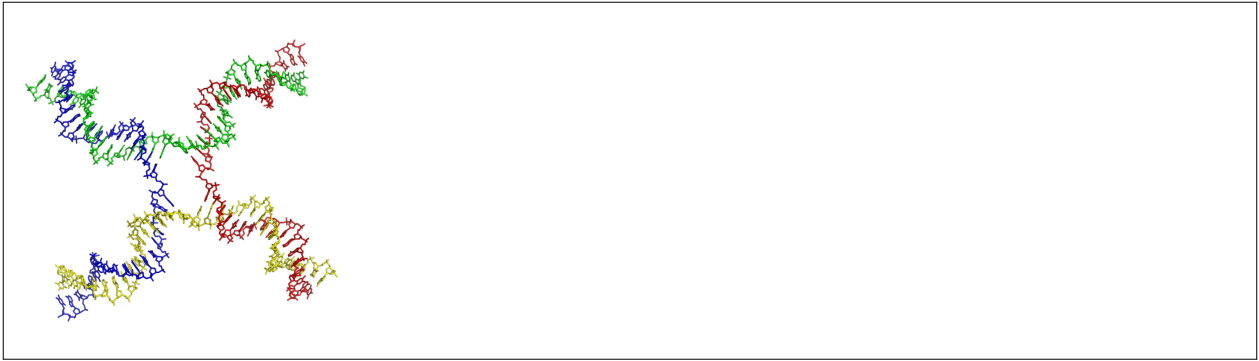
Structure of the Holliday junction intermediate in genetic recombination. The four separate DNA strands are coloured red, blue, green and yellow.[96]

Recombination involves the breakage and rejoining of two chromosomes (M and F) to produce two re-arranged chromosomes (C1 and C2).
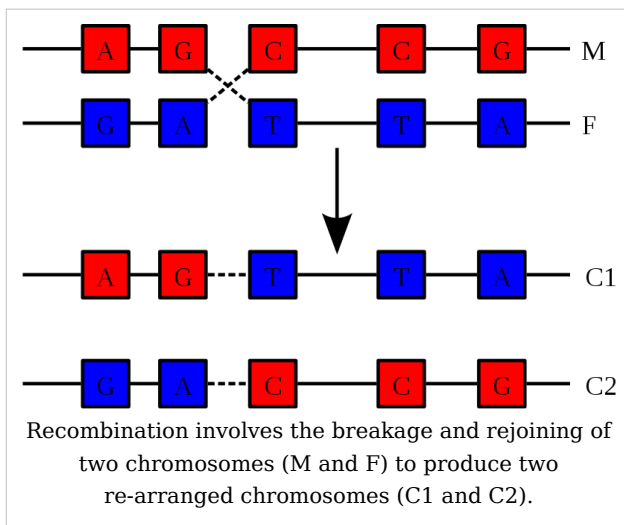
A DNA helix usually does not interact with other segments of DNA, and in human cells the different chromosomes even occupy separate areas in the nucleus called "chromosome territories".[97] This physical separation of different chromosomes is important for the ability of DNA to function as a stable repository for information, as one of the few times chromosomes interact is during chromosomal crossover when they recombine. Chromosomal crossover is when two DNA helices break, swap a section and then rejoin.

Recombination allows chromosomes to exchange genetic information and produces new combinations of genes, which increases the efficiency of natural selection and can be important in the rapid evolution of new proteins.[98] Genetic recombination can also be involved in DNA repair, particularly in the cell's response to double-strand breaks.[99]

The most common form of chromosomal crossover is homologous recombination, where the two chromosomes involved share very similar sequences. Non-homologous recombination can be damaging to cells, as it can produce chromosomal translocations and genetic abnormalities. The recombination reaction is catalyzed by enzymes known as *recombinases*, such as RAD51.[100] The first step in recombination is a double-stranded break either caused by an endonuclease or damage to the DNA.[101] A series of steps catalyzed in part by the recombinase then leads to joining of the two helices by at least one Holliday junction, in which a segment of a single strand in each helix is annealed to the complementary strand in the other helix. The Holliday junction is a tetrahedral junction structure that can be moved along the pair of chromosomes, swapping one strand for another. The recombination reaction is then halted by cleavage of the junction and re-ligation of the released DNA.[102]

Evolution

DNA contains the genetic information that allows all modern living things to function, grow and reproduce. However, it is unclear how long in the 4-billion-year history of life DNA has performed this function, as it has been proposed that the earliest forms of life may have used RNA as their genetic material.[91] [103] RNA may have acted as the central part of early cell metabolism as it can both transmit genetic information and carry out catalysis as part of ribozymes.[104] This ancient RNA world where nucleic acid would have been used for both catalysis and genetics may have influenced the evolution of the current genetic code based on four nucleotide bases. This would occur since the number of unique bases in such an organism is a trade-off between a small number of bases increasing replication accuracy and a large number of bases increasing the catalytic efficiency of ribozymes.[105]

Unfortunately, there is no direct evidence of ancient genetic systems, as recovery of DNA from most fossils is impossible. This is because DNA will survive in the environment for less than one million years and slowly degrades into short fragments in solution.[106] Claims for older DNA have been made, most notably a report of the isolation of a viable bacterium from a salt crystal 250-million years old,[107] but these claims are controversial.[108] [109]

Uses in technology

Genetic engineering

Methods have been developed to purify DNA from organisms, such as phenol-chloroform extraction and manipulate it in the laboratory, such as restriction digests and the polymerase chain reaction. Modern biology and biochemistry make intensive use of these techniques in recombinant DNA technology. Recombinant DNA is a man-made DNA sequence that has been assembled from other DNA sequences. They can be transformed into organisms in the form of plasmids or in the appropriate format, by using a viral vector.[110] The genetically modified organisms produced can be used to produce products such as recombinant proteins, used in medical research,[111] or be grown in agriculture.[112] [113]

Forensics

Forensic scientists can use DNA in blood, semen, skin, saliva or hair found at a crime scene to identify a matching DNA of an individual, such as a perpetrator. This process is called genetic fingerprinting, or more accurately, DNA profiling. In DNA profiling, the lengths of variable sections of repetitive DNA, such as short tandem repeats and minisatellites, are compared between people. This method is usually an extremely reliable technique for identifying a matching DNA.[114] However, identification can be complicated if the scene is contaminated with DNA from several people.[115] DNA profiling was developed in 1984 by British geneticist Sir Alec Jeffreys,[116] and first used in forensic science to convict Colin Pitchfork in the 1988 Enderby murders case.[117]

People convicted of certain types of crimes may be required to provide a sample of DNA for a database. This has helped investigators solve old cases where only a DNA sample was obtained from the scene. DNA profiling can also be used to identify victims of mass casualty incidents.[118] On the other hand, many convicted people have been released from prison on the basis of DNA techniques, which were not available when a crime had originally been committed.

Bioinformatics

Bioinformatics involves the manipulation, searching, and data mining of DNA sequence data. The development of techniques to store and search DNA sequences have led to widely applied advances in computer science, especially string searching algorithms, machine learning and database theory.[119] String searching or matching algorithms, which find an occurrence of a sequence of letters inside a larger sequence of letters, were developed to search for specific sequences of nucleotides.[120] In other applications such as text editors, even simple algorithms for this problem usually suffice, but DNA sequences cause these algorithms to exhibit near-worst-case behaviour due to their small number of distinct characters. The related problem of sequence alignment aims to identify homologous sequences and locate the specific mutations that make them distinct. These techniques, especially multiple sequence alignment, are used in studying phylogenetic relationships and protein function.[121] Data sets representing entire genomes' worth of DNA sequences, such as those produced by the Human Genome Project, are difficult to use without annotations, which label the locations of genes and regulatory elements on each chromosome. Regions of DNA sequence that have the characteristic patterns associated with protein- or RNA-coding genes can be identified by gene finding algorithms, which allow researchers to predict the presence of particular gene products in an organism even before they have been isolated experimentally.[122]

DNA nanotechnology

DNA nanotechnology uses the unique molecular recognition properties of DNA and other nucleic acids to create self-assembling branched DNA complexes with useful properties.[124] DNA is thus used as a structural material rather than as a carrier of biological information. This has led to the creation of two-dimensional periodic lattices (both tile-based as well as using the "DNA origami" method) as well as three-dimensional structures in the shapes of

The DNA structure at left (schematic shown) will self-assemble into the structure visualized by atomic force microscopy at right. DNA nanotechnology is the field which seeks to design nanoscale structures using the molecular recognition properties of DNA molecules. Image from Strong, 2004.[123]

polyhedra.[125] Nanomechanical devices and algorithmic self-assembly have also been demonstrated,[126] and these DNA structures have been used to template the arrangement of other molecules such as gold nanoparticles and streptavidin proteins.[127]
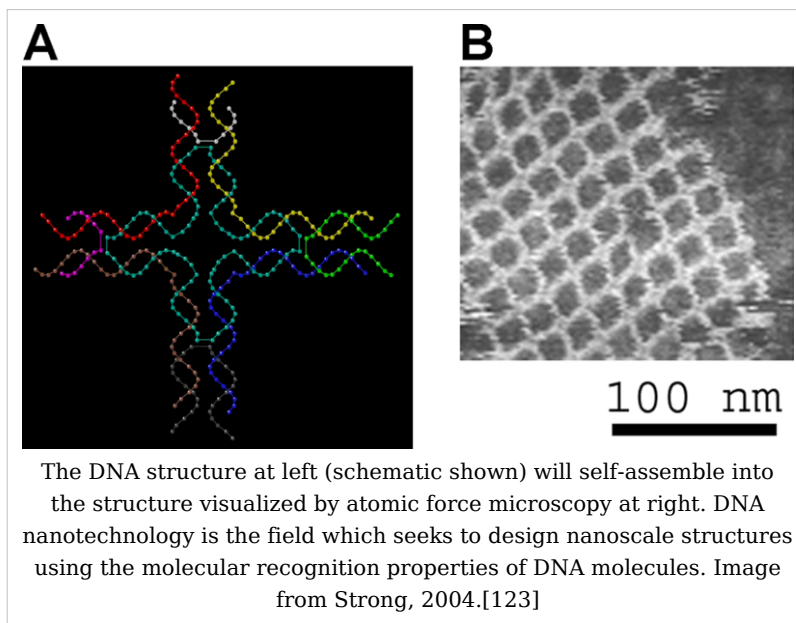
History and anthropology

Because DNA collects mutations over time, which are then inherited, it contains historical information and by comparing DNA sequences, geneticists can infer the evolutionary history of organisms, their phylogeny.[128] This field of phylogenetics is a powerful tool in evolutionary biology. If DNA sequences within a species are compared, population geneticists can learn the history of particular populations. This can be used in studies ranging from ecological genetics to anthropology; for example, DNA evidence is being used to try to identify the Ten Lost Tribes of Israel.[129] [130]

DNA has also been used to look at modern family relationships, such as establishing family relationships between the descendants of Sally Hemings and Thomas Jefferson. This usage is closely related to the use of DNA in criminal investigations detailed above. Indeed, some criminal investigations have been solved when DNA from crime scenes has matched relatives of the guilty individual.[131]

History of DNA research

DNA was first isolated by the Swiss physician Friedrich Miescher who, in 1869, discovered a microscopic substance in the pus of discarded surgical bandages. As it resided in the nuclei of cells, he called it "nuclein".[132] In 1919, Phoebus Levene identified the base, sugar and phosphate nucleotide unit.[133] Levene suggested that DNA consisted of a string of nucleotide units linked together through the phosphate groups. However, Levene thought the chain was short and the bases repeated in a fixed order. In 1937 William Astbury produced the first X-ray diffraction patterns that showed that DNA had a regular structure.[134]

In 1928, Frederick Griffith discovered that traits of the "smooth" form of the *Pneumococcus* could be transferred to the "rough" form of the same bacteria by mixing killed "smooth" bacteria with the live "rough" form.[135] This system provided the first clear suggestion that DNA carried genetic information—the Avery-MacLeod-McCarty experiment—when Oswald Avery, along with coworkers Colin MacLeod and Maclyn McCarty, identified DNA as the transforming principle in 1943.[136] DNA's role in heredity was confirmed in 1952, when Alfred Hershey and Martha Chase in the Hershey-Chase experiment showed that DNA is the genetic material of the T2 phage.[137]
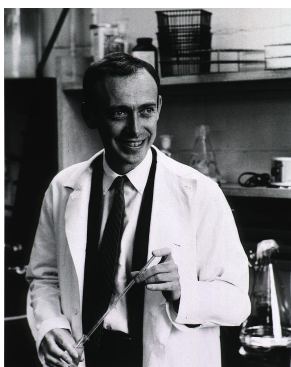
James D. Watson
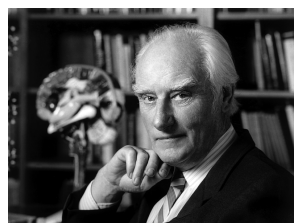
Francis Crick

Francis Crick

Rosalind Franklin

Raymond Gosling

Maurice F. Wilkins

Erwin Chargaff

DNA Helix controversy
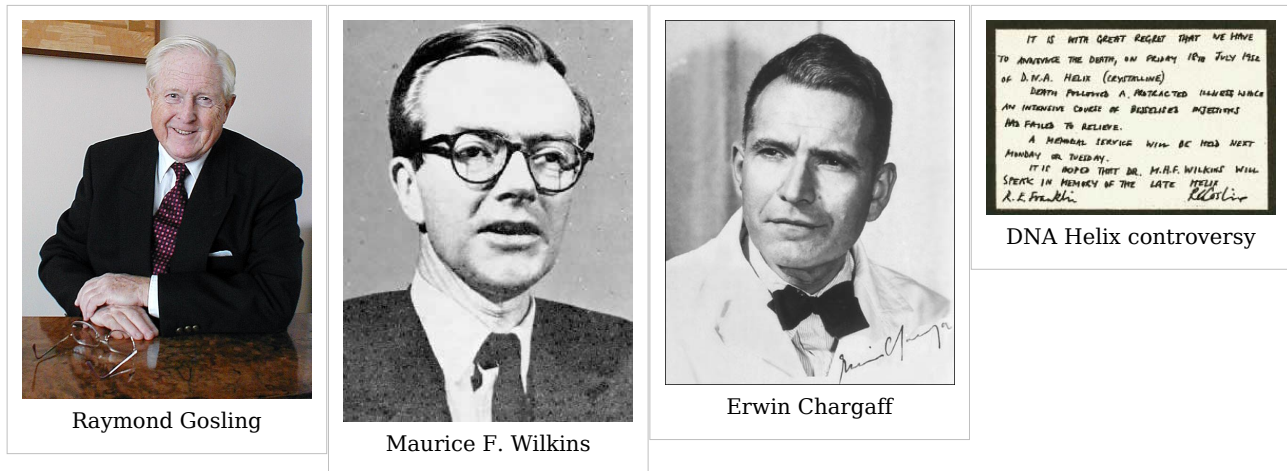
In 1953 James D. Watson and Francis Crick suggested what is now accepted as the first correct double-helix model of DNA structure in the journal *Nature*.[7] Their double-helix, molecular model of DNA was then based on a single X-ray diffraction image (labeled as "Photo 51")[138] taken by Rosalind Franklin and Raymond Gosling in May 1952, as well as the information that the DNA bases were paired—also obtained through private communications from Erwin Chargaff in the previous years. Chargaff's rules played a very important role in establishing double-helix configurations for B-DNA as well as A-DNA.

Experimental evidence supporting the Watson and Crick model were published in a series of five articles in the same issue of *Nature*.[139] Of these, Franklin and Gosling's paper was the first publication of their own X-ray diffraction data and original analysis method that partially supported the Watson and Crick model[30] [140] ; this issue also contained an article on DNA structure by Maurice Wilkins and two of his colleagues, whose analysis and *in vivo* B-DNA X-ray patterns also supported the presence *in vivo* of the double-helical DNA configurations as proposed by Crick and Watson for their double-helix molecular model of DNA in the previous two pages of *Nature*.[31] In 1962, after Franklin's death, Watson, Crick, and Wilkins jointly received the Nobel Prize in Physiology or Medicine.[141] Unfortunately, Nobel rules of the time allowed only living recipients, but a vigorous debate continues on who should receive credit for the discovery.[142]

In an influential presentation in 1957, Crick laid out the "Central Dogma" of molecular biology, which foretold the relationship between DNA, RNA, and proteins, and articulated the "adaptor hypothesis".[143] Final confirmation of the replication mechanism that was implied by the double-helical structure followed in 1958 through the Meselson-Stahl experiment.[144] Further work by Crick and coworkers showed that the genetic code was based on non-overlapping triplets of bases, called codons, allowing Har Gobind Khorana, Robert W. Holley and Marshall Warren Nirenberg to decipher the genetic code.[145] These findings represent the birth of molecular biology.

See also

- Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid
- Molecular models of DNA
- DNA microarray
- DNA sequencing
- Paracrystal model and theory
- X-ray scattering
- Crystallography
- X-ray crystallography
- Genetic disorder
- Junk DNA
- Nucleic acid analogues
- Nucleic acid methods
- Nucleic acid modeling
- Nucleic Acid Notations
- Phosphoramidite
- Plasmid
- Polymerase chain reaction
- *Proteopedia DNA* [146]
- Southern blot
- Triple-stranded DNA

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[138] The B-DNA X-ray pattern on the right of this linked image (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/pictures/sci9.001.5.html) was obtained by Rosalind Franklin and Raymond Gosling in May 1952 at high hydration levels of DNA and it has been labeled as "Photo 51"

[139] Nature Archives Double Helix of DNA: 50 Years (http://www.nature.com/nature/dna50/archive.html)

[140] Original X-ray diffraction image (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/pictures/franklin-typeBphoto.html)

[141] The Nobel Prize in Physiology or Medicine 1962 (http://nobelprize.org/nobel_prizes/medicine/laureates/1962/) Nobelprize .org Accessed 22 December 06

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[146] http://proteopedia.org/wiki/index.php/DNA

Further reading

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- Dennis, Carina; Julie Clayton (2003). *50 years of DNA*. Basingstoke: Palgrave Macmillan. ISBN 1-4039-1479-6.
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- Olby, Robert C. (2009). *Francis Crick: A Biography*. Plainview, N.Y: Cold Spring Harbor Laboratory Press. ISBN 0-87969-798-9.
- Ridley, Matt (2006). *Francis Crick: discoverer of the genetic code*. [Ashland, OH: Eminent Lives, Atlas Books. ISBN 0-06-082333-X.
- Berry, Andrew; Watson, James D. (2003). *DNA: the secret of life*. New York: Alfred A. Knopf. ISBN 0-375-41546-7.

- Stent, Gunther Siegmund; Watson, James D. (1980). *The double helix: a personal account of the discovery of the structure of DNA*. New York: Norton. ISBN 0-393-95075-1.
- Wilkins, Maurice (2003). *The third man of the double helix the autobiography of Maurice Wilkins*. Cambridge, Eng: University Press. ISBN 0-19-860665-6.

External links

- DNA (http://www.dmoz.org/Science/Biology/Biochemistry_and_Molecular_Biology/ Biomolecules/Nucleic_Acids/DNA//) at the Open Directory Project
- DNA binding site prediction on protein (http://pipe.scs.fsu.edu/displar.html)
- DNA coiling to form chromosomes (http://biostudio.com/c_ education mac.htm)
- DNA from the Beginning (http://www.dnaftb.org/dnaftb/) Another DNA Learning Center site on DNA, genes, and heredity from Mendel to the human genome project.
- DNA Lab, demonstrates how to extract DNA from wheat using readily available equipment and supplies. (http://ca.youtube.com/watch?v=iyb7fwduuGM)
- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/ dna_double_helix/) From the official Nobel Prize web site
- DNA under electron microscope (http://www.fidelitysystems.com/Unlinked_DNA. html)
- Dolan DNA Learning Center (http://www.dnalc.org/)
- Double Helix: 50 years of DNA (http://www.nature.com/nature/dna50/archive.html), *Nature*
- Double Helix 1953–2003 (http://www.ncbe.reading.ac.uk/DNA50/) National Centre for Biotechnology Education
- Francis Crick and James Watson talking on the BBC in 1962, 1972, and 1974 (http:// www.bbc.co.uk/bbcfour/audiointerviews/profilepages/crickwatson1.shtml)
- Genetic Education Modules for Teachers (http://www.genome.gov/10506718) — *DNA from the Beginning* Study Guide
- Guide to DNA cloning (http://www.blackwellpublishing.com/trun/artwork/ Animations/cloningexp/cloningexp.html)
- Olby R (January 2003). "http://chem-faculty.ucsd.edu/joseph/CHEM13/DNA1.pdf|Quiet debut for the double helix". *Nature* **421** (6921): 402–5. doi: 10.1038/nature01397 (http:// dx.doi.org/10.1038/nature01397). PMID 12540907. http://chem-faculty.ucsd.edu/ joseph/CHEM13/DNA1.pdf.
- PDB Molecule of the Month *pdb23_1* (http://www.rcsb.org/pdb/static. do?p=education_discussion/molecule_of_the_month/pdb23_1.html)
- Rosalind Franklin's contributions to the study of DNA (http://mason.gmu.edu/ ~emoody/rfranklin.html)
- The Register of Francis Crick Personal Papers 1938 - 2007 (http://orpheus.ucsd.edu/ speccoll/testing/html/mss0660a.html#abstract) at Mandeville Special Collections Library, Geisel Library, University of California, San Diego
- U.S. National DNA Day (http://www.genome.gov/10506367) — watch videos and participate in real-time chat with top scientists
- "http://www.nytimes.com/packages/pdf/science/dna-article.pdf|Clue to chemistry of heredity found". *The New York Times*. Saturday, June 13, 1953. http://www.nytimes. com/packages/pdf/science/dna-article.pdf. The first American newspaper coverage of the discovery of the DNA structure.
- (http://www.elmhurst.edu/~chm/vchembook/581nucleotides.html)

Molecular models of DNA

Molecular models of DNA structures are representations of the molecular geometry and topology of Deoxyribonucleic acid (DNA) molecules using one of several means, such as: closely packed spheres (CPK models) made of plastic, metal wires for 'skeletal models', graphic computations and animations by computers, artistic rendering, and so on, with the aim of simplifying and presenting the essential, physical and chemical, properties of DNA molecular structures either *in vivo* or *in vitro*. Computer molecular models also allow animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*. Thus, an old standing dynamic problem is how DNA "self-replication" takes place in living cells that should involve transient uncoiling of supercoiled DNA fibers. Although DNA consists of relatively rigid, very large elongated biopolymer molecules called "fibers" or chains (that are made of repeating nucleotide units of four basic types, attached to deoxyribose and phosphate groups), its molecular structure *in vivo* undergoes dynamic configuration changes that involve dynamically attached water molecules and ions. Supercoiling, packing with histones in chromosome structures, and other such supramolecular aspects also involve *in vivo* DNA topology which is even more complex than DNA molecular geometry, thus turning molecular modeling of DNA into an especially challenging problem for both molecular biologists and biotechnologists. Like other large molecules and biopolymers, DNA often exists in multiple stable geometries (that is, it exhibits conformational isomerism) and configurational, quantum states which are close to each other in energy on the potential energy surface of the DNA molecule. Such geometries can also be computed, at least in principle, by employing *ab initio* quantum chemistry methods that have high accuracy for small molecules. Such quantum geometries define an important class of *ab initio* molecular models of DNA whose exploration has barely started.

In an interesting twist of roles, the DNA molecule itself was proposed to be utilized for quantum computing. Both DNA nanostructures as well as DNA 'computing' biochips have been built (see biochip image at right).

DNA computing biochip:3D

The more advanced, computer-based molecular models of DNA involve molecular dynamics simulations as well as quantum mechanical computations of vibro-rotations, delocalized molecular orbitals (MOs), electric dipole moments, hydrogen-bonding, and so on.
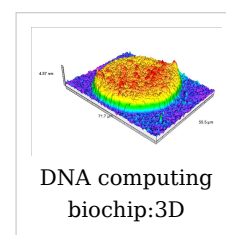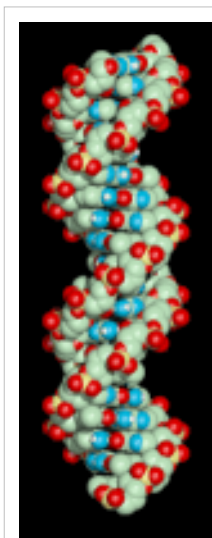
Importance

Spinning DNA generic model.

From the very early stages of structural studies of DNA by X-ray diffraction and biochemical means, molecular models such as the Watson-Crick double-helix model were successfully employed to solve the 'puzzle' of DNA structure, and also find how the latter relates to its key functions in living cells. The first high quality X-ray diffraction patterns of A-DNA were reported by Rosalind Franklin and Raymond Gosling in 1953[1] . The first calculations of the Fourier transform of an atomic helix were reported one year earlier by Cochran, Crick and Vand [2] , and were followed in 1953 by the computation of the Fourier transform of a coiled-coil by Crick[3] . The first reports of a double-helix molecular model of B-DNA structure were made by Watson and Crick in 1953[4] [5] . Last-but-not-least, Maurice F. Wilkins, A. Stokes and H.R. Wilson, reported the first X-ray patterns of *in vivo* B-DNA in partially oriented salmon sperm heads [6] . The development of the first correct double-helix molecular model of DNA by Crick and Watson may not have been possible without the biochemical evidence for the nucleotide base-pairing ([A---T]; [C---G]), or Chargaff's rules[7] [8] [9] [10] [11] [12] .

Examples of DNA molecular models

Animated molecular models allow one to visually explore the three-dimensional (3D) structure of DNA. The first DNA model is a space-filling, or CPK, model of the DNA double-helix whereas the third is an animated wire, or skeletal type, molecular model of DNA. The last two DNA molecular models in this series depict quadruplex DNA [13] that may be involved in certain cancers[14] [15] . The last figure on this panel is a molecular model of hydrogen bonds between water molecules in ice that are similar to those found in DNA.
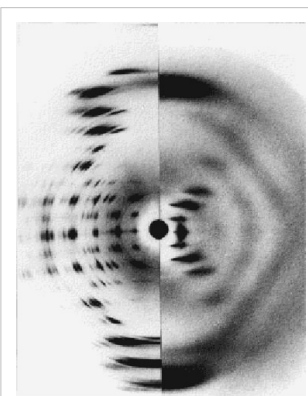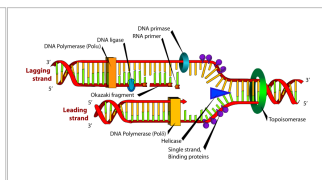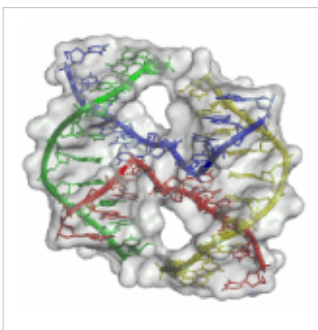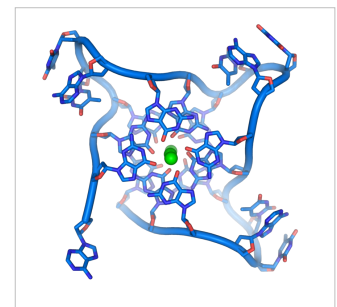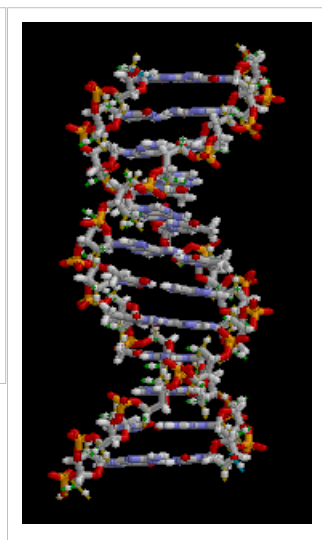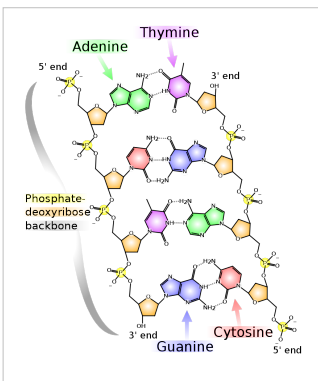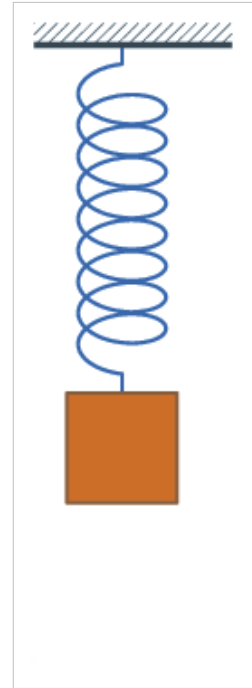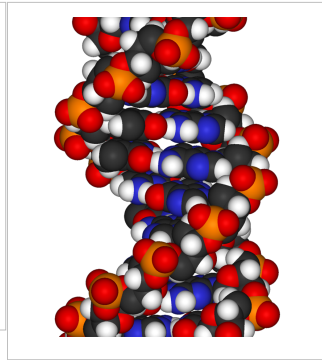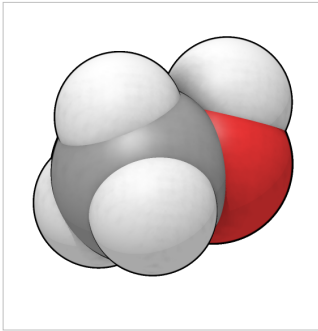
A-DNA   B-DNA
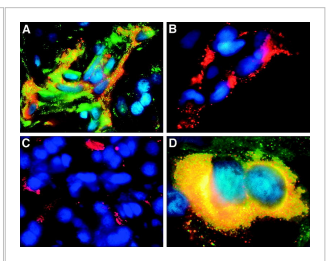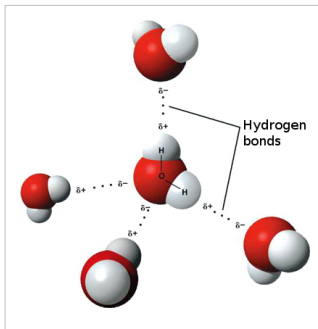
- Spacefilling model or CPK model - a molecule is represented by overlapping spheres representing the atoms.

DNA Spacefilling molecular model
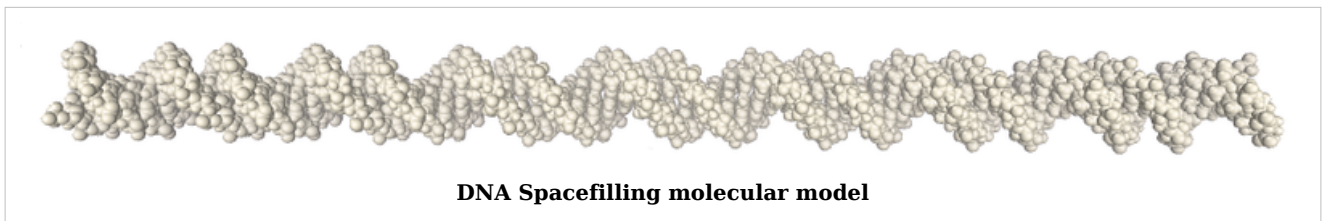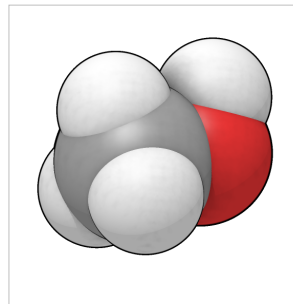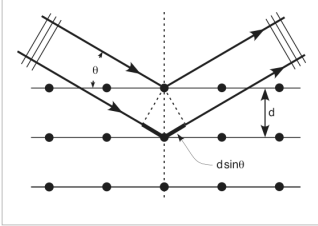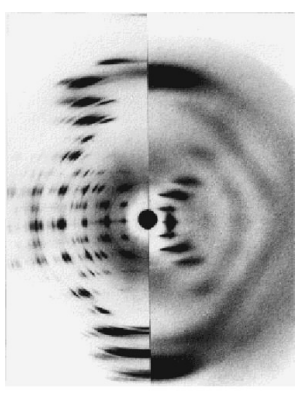
Images for DNA Structure Determination from X-Ray Patterns

The following images illustrate both the principles and the main steps involved in generating structural information from X-ray diffraction studies of oriented DNA fibers with the help of molecular models of DNA that are combined with crystallographic and mathematical analysis of the X-ray patterns. From left to right the gallery of images shows:

- *First row*:
- 1. Constructive X-ray interference, or diffraction, following Bragg's Law of X-ray "*reflection by the crystal planes*";
- 2. A comparison of A-DNA (crystalline) and highly hydrated B-DNA (paracrystalline) X-ray diffraction, and respectively, X-ray scattering patterns (courtesy of Dr. Herbert R. Wilson, FRS- see refs. list);
- 3. Purified DNA precipitated in a water jug;
- 4. The major steps involved in DNA structure determination by X-ray crystallography showing the important role played by molecular models of DNA structure in this iterative, structure--determination process;
- *Second row*:
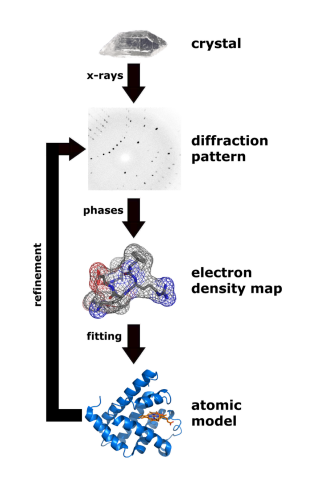
- 5. Photo of a modern X-ray diffractometer employed for recording X-ray patterns of DNA with major components: X-ray source, goniometer, sample holder, X-ray detector and/or plate holder;
- 6. Illustrated animation of an X-ray goniometer;
- 7. X-ray detector at the SLAC synchrotron facility;
- 8. Neutron scattering facility at ISIS in UK;
  - *Third and fourth rows*: *Molecular models of DNA structure at various scales*; figure #11 is an actual electron micrograph of a DNA fiber bundle, presumably of a single bacterial chromosome loop.
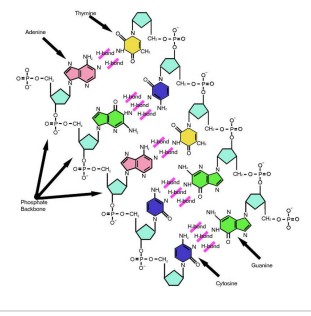
Paracrystalline lattice models of B-DNA structures

A paracrystalline lattice, or paracrystal, is a molecular or atomic lattice with significant amounts (e.g., larger than a few percent) of partial disordering of molecular arranegements. Limiting cases of the paracrystal model are nanostructures, such as glasses, liquids, etc., that may possess only local ordering and no global order. Liquid crystals also have paracrystalline rather than crystalline structures.

DNA Helix controversy in 1952
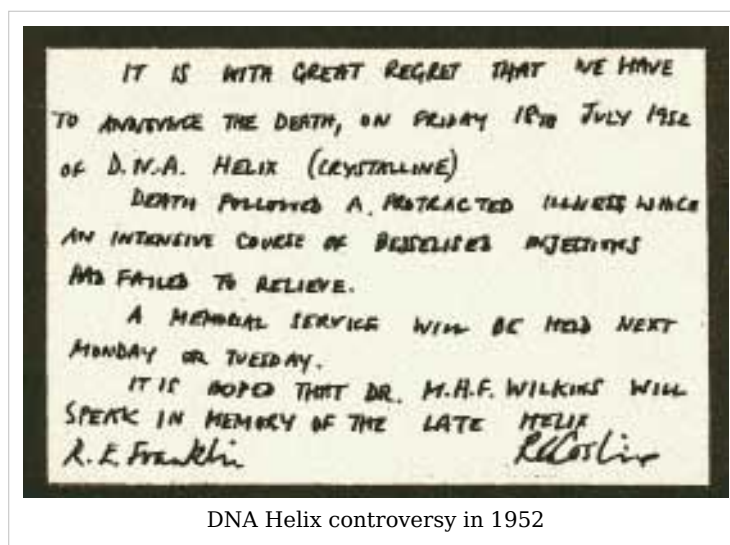
Highly hydrated B-DNA occurs naturally in living cells in such a paracrystalline state, which is a dynamic one in spite of the relatively rigid DNA double-helix stabilized by parallel hydrogen bonds between the nucleotide base-pairs in the two complementary, helical DNA chains (see figures). For simplicity most DNA molecular models ommit both water and ions dynamically bound to B-DNA, and are thus less useful for understanding the dynamic behaviors of B-DNA *in vivo*. The physical and mathematical analysis of X-ray[16] [17] and spectroscopic data for paracrystalline B-DNA is therefore much more complicated than that of crystalline, A-DNA X-ray diffraction patterns. The paracrystal model is also important for DNA technological applications such as DNA nanotechnology. Novel techniques that combine X-ray diffraction of DNA with X-ray microscopy in hydrated living cells are now also being developed (see, for example, "Application of X-ray microscopy in the analysis of living hydrated cells" [18]).

Genomic and Biotechnology Applications of DNA molecular modeling

The following gallery of images illustrates various uses of DNA molecular modeling in Genomics and Biotechnology research applications from DNA repair to PCR and DNA nanostructures; each slide contains its own explanation and/or details. The first slide presents an overview of DNA applications, including DNA molecular models, with emphasis on Genomics and Biotechnology.

Gallery: DNA Molecular modeling applications
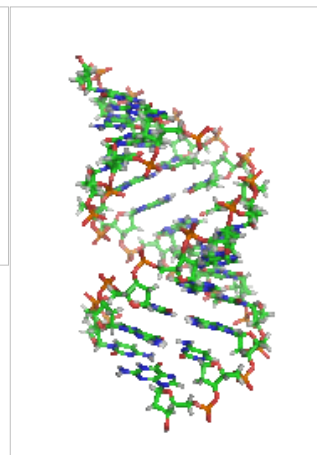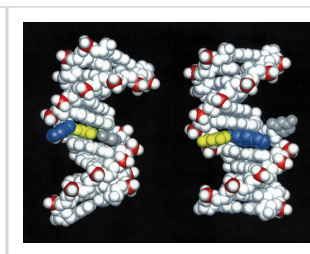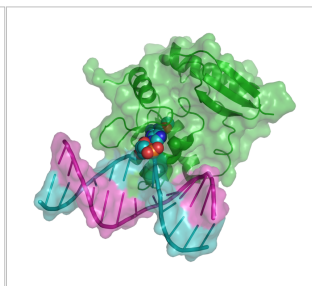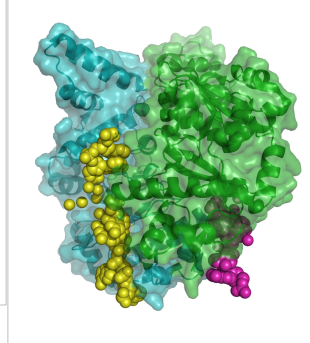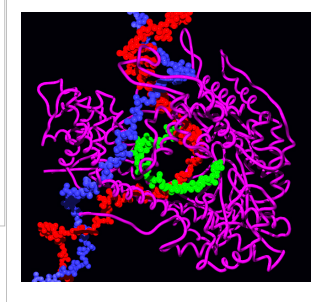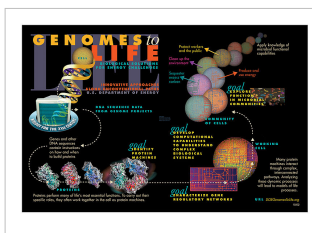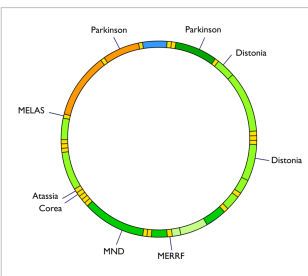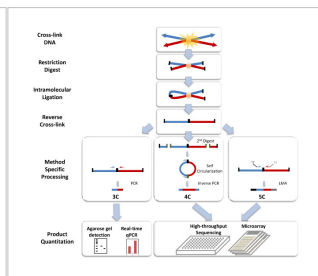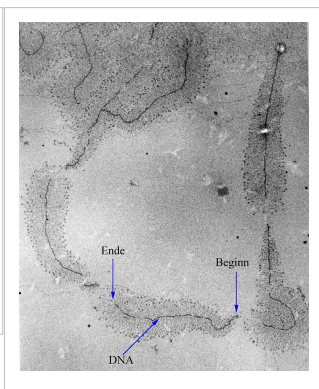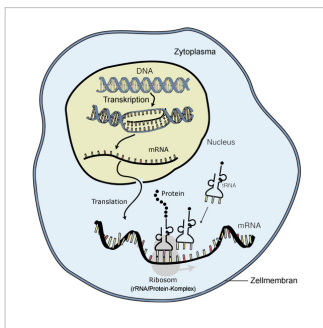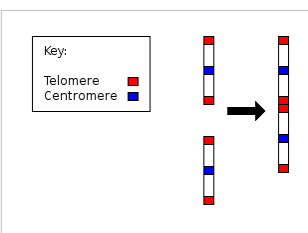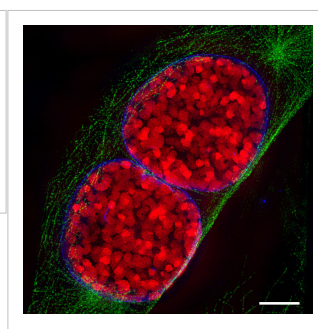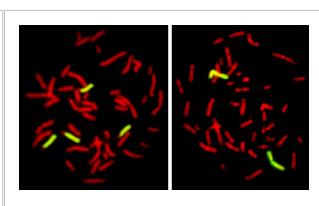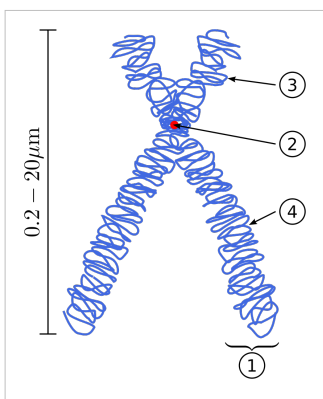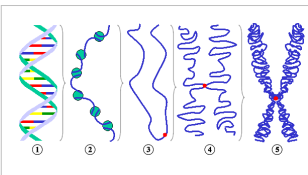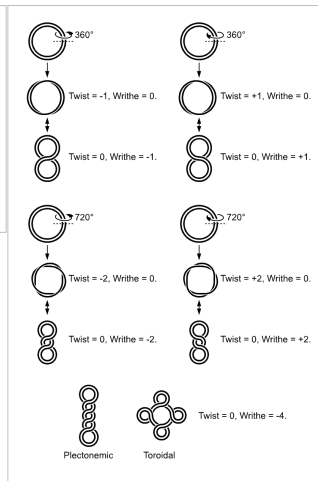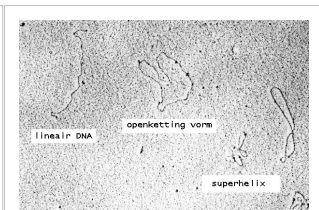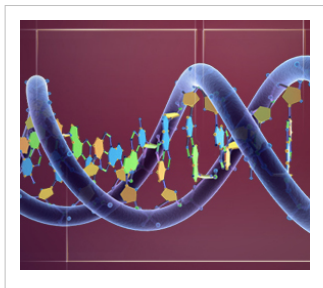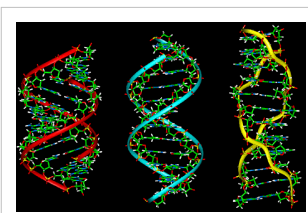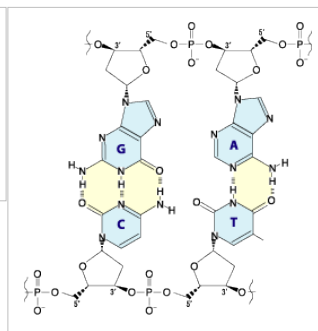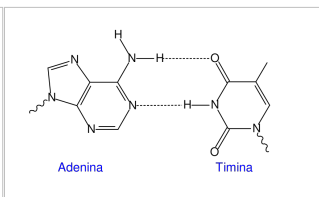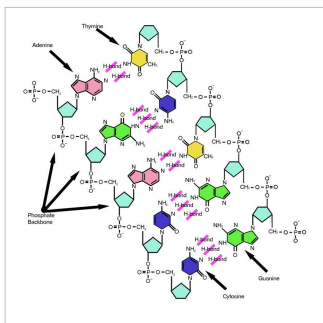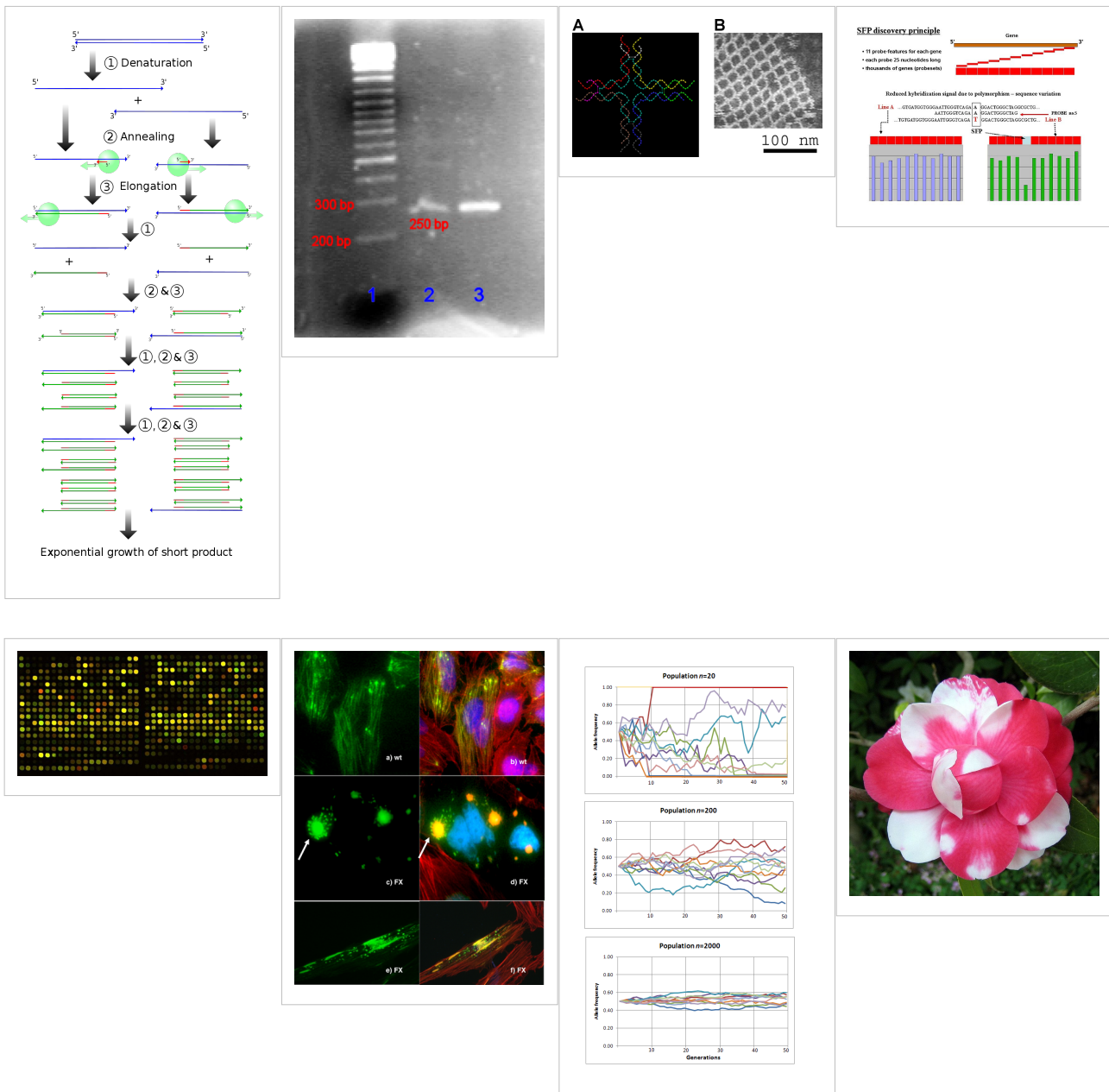
Databases for DNA molecular models and sequences

X-ray diffraction

- NDB ID: UD0017 Database [13]
- X-ray Atlas -database [19]
- PDB files of coordinates for nucleic acid structures from X-ray diffraction by NA (incl. DNA) crystals [20]
- Structure factors dowloadable files in CIF format [21]

Neutron scattering

- ISIS neutron source
- ISIS pulsed neutron source:A world centre for science with neutrons & muons at Harwell, near Oxford, UK. [22]

X-ray microscopy

- Application of X-ray microscopy in the analysis of living hydrated cells [18]

Electron microscopy

- DNA under electron microscope [23]

Atomic Force Microscopy (AFM)

Two-dimensional DNA junction arrays have been visualized by Atomic Force Microscopy (AFM)[24] . Other imaging resources for AFM/Scanning probe microscopy(SPM) can be freely accessed at:

- How SPM Works [25]
- SPM Image Gallery - AFM STM SEM MFM NSOM and more. [26]

Gallery of AFM Images
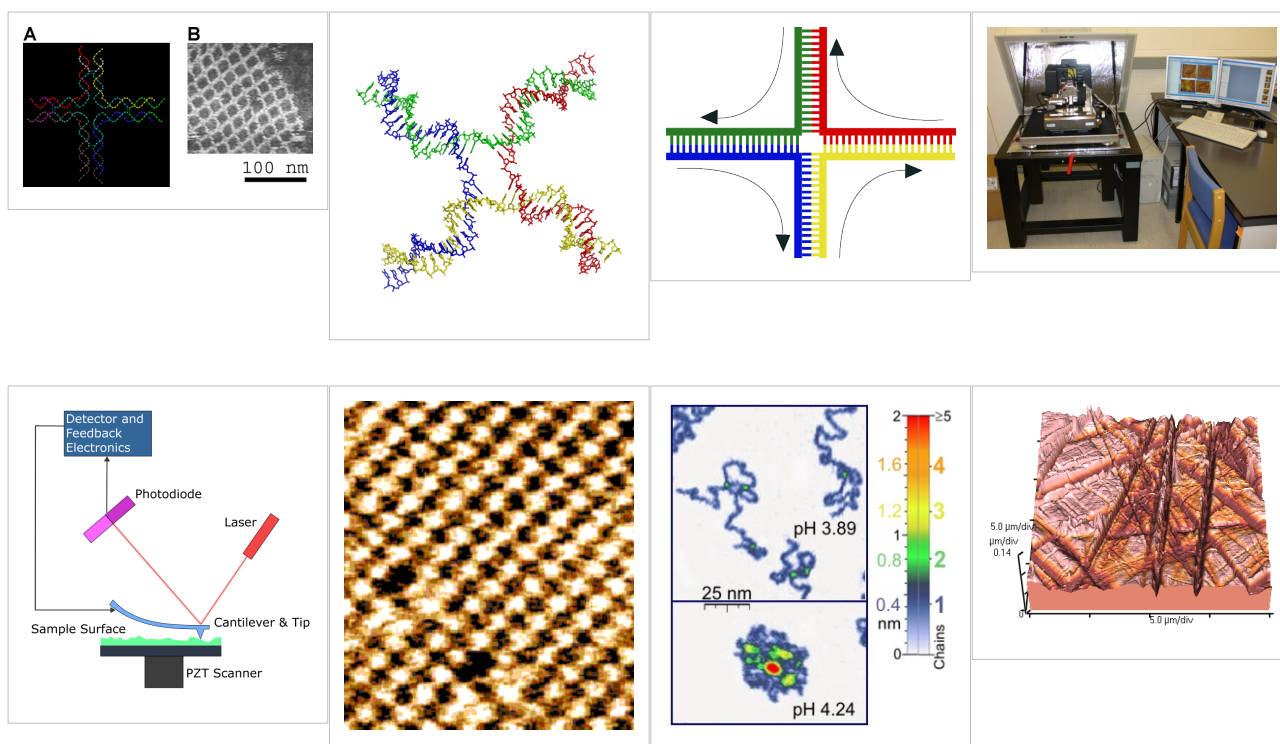
Mass spectrometry--Maldi informatics
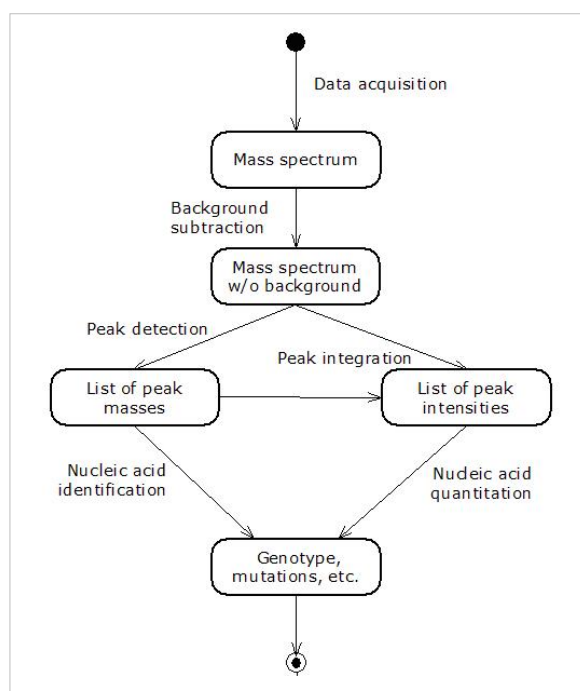
Spectroscopy

- Vibrational circular dichroism (VCD)
- FT-NMR[27] [28]
  - NMR Atlas--database [29]
  - mmcif downloadable coordinate files of nucleic acids in solution from 2D-FT NMR data [30]
  - NMR constraints files for NAs in PDB format [31]
- NMR microscopy[32]
- Microwave spectroscopy
- FT-IR
- FT-NIR[33] [34] [35]
- Spectral, Hyperspectral, and Chemical imaging)[36] [37] [38] [39] [40] [41] [42] .
- Raman spectroscopy/microscopy[43] and CARS[44] .
- Fluorescence correlation spectroscopy[45] [46] [47] [48] [49] [50] [51] [52] , Fluorescence cross-correlation spectroscopy and FRET[53] [54] [55] .
- Confocal microscopy[56]

Gallery: CARS (Raman spectroscopy), Fluorescence confocal microscopy, and Hyperspectral imaging
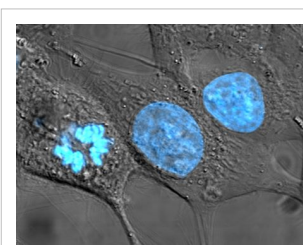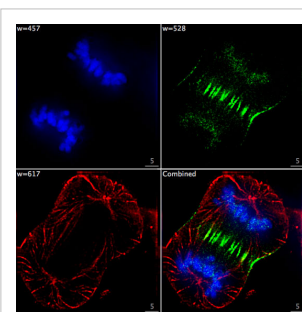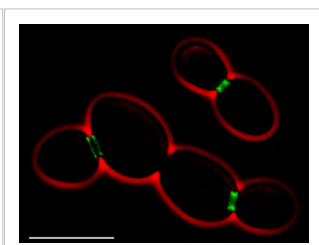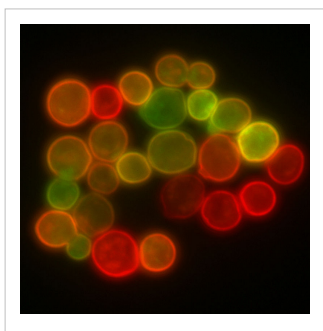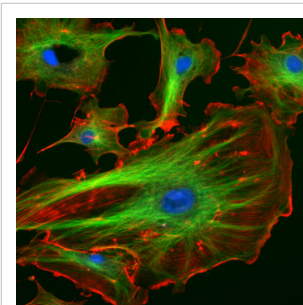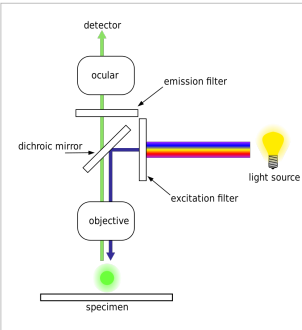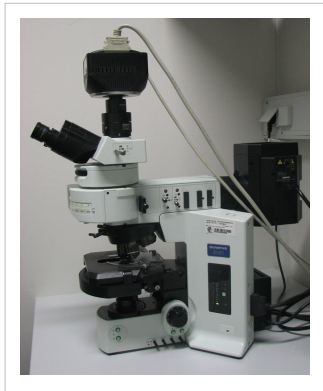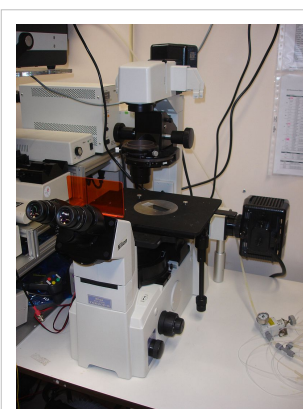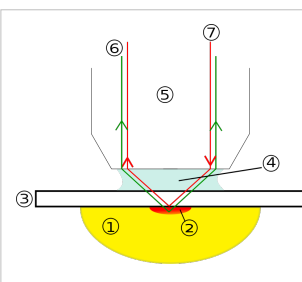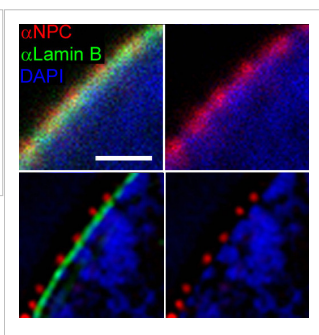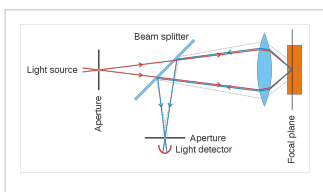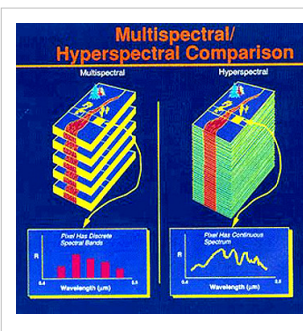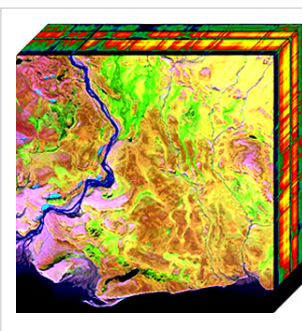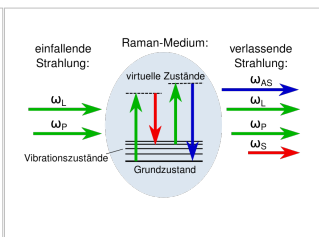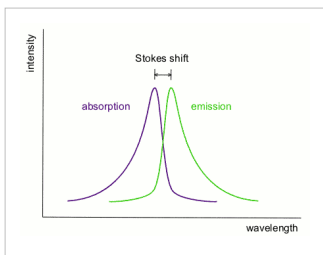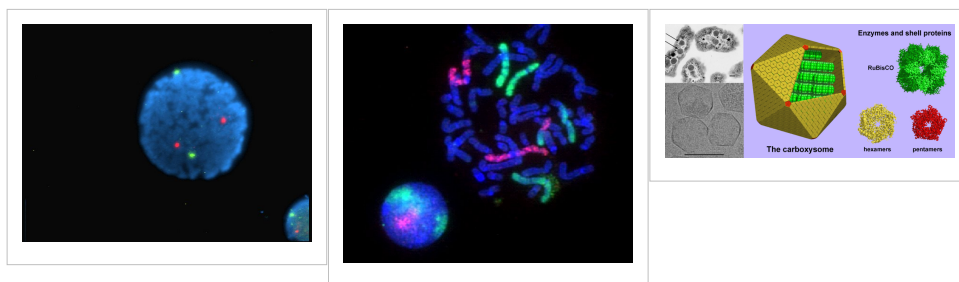
Genomic and structural databases

- CBS Genome Atlas Database [57] — contains examples of base skews.[58]
- The Z curve database of genomes — a 3-dimensional visualization and analysis tool of genomes [59][60] .
- DNA and other nucleic acids' molecular models: Coordinate files of nucleic acids molecular structure models in PDB and CIF formats [61]

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See also

- DNA
- Molecular graphics
- DNA structure
- DNA Dynamics
- X-ray scattering
- Neutron scattering
- Crystallography
- Crystal lattices
- Paracrystalline lattices/Paracrystals
- 2D-FT NMRI and Spectroscopy
- NMR Spectroscopy
- Microwave spectroscopy
- Two-dimensional IR spectroscopy
- Spectral imaging
- Hyperspectral imaging
- Chemical imaging
- NMR microscopy
- VCD or Vibrational circular dichroism
- FRET and FCS- Fluorescence correlation spectroscopy
- Fluorescence cross-correlation spectroscopy (FCCS)
- Molecular structure
- Molecular geometry
- Molecular topology
- DNA topology
- Sirius visualization software
- Nanostructure
- DNA nanotechnology
- Imaging
- Atomic force microscopy
- X-ray microscopy
- Liquid crystal
- Glasses
- QMC@Home
- Sir Lawrence Bragg, FRS
- Sir John Randall
- James Watson
- Francis Crick
- Maurice Wilkins
- Herbert Wilson, FRS
- Alex Stokes

External links

- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/dna_double_helix/) From the official Nobel Prize web site
- MDDNA: Structural Bioinformatics of DNA (http://humphry.chem.wesleyan.edu:8080/MDDNA/)
- Double Helix 1953–2003 (http://www.ncbe.reading.ac.uk/DNA50/) National Centre for Biotechnology Education
- DNA under electron microscope (http://www.fidelitysystems.com/Unlinked_DNA.html)
- Ascalaph DNA (http://www.agilemolecule.com/Ascalaph/Ascalaph_DNA.html) — Commercial software for DNA modeling
- DNAlive: a web interface to compute DNA physical properties (http://mmb.pcb.ub.es/DNAlive). Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- DiProDB: Dinucleotide Property Database (http://diprodb.fli-leibniz.de). The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.
- Further details of mathematical and molecular analysis of DNA structure based on X-ray data (http://planetphysics.org/encyclopedia/BesselFunctionsApplicationsToDiffractionByHelicalStructures.html)
- Bessel functions corresponding to Fourier transforms of atomic or molecular helices. (http://planetphysics.org/?op=getobj&from=objects&name=BesselFunctionsAndTheirApplicationsToDiffractionByHelicalStructures)
- Application of X-ray microscopy in analysis of living hydrated cells (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938)
- Characterization in nanotechnology some pdfs (http://nanocharacterization.sitesled.com/)
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- How SPM Works (http://www.parkafm.com/New_html/resources/01general.php)
- U.S. National DNA Day (http://www.genome.gov/10506367) — watch videos and participate in real-time discussions with scientists.
- The Secret Life of DNA - DNA Music compositions (http://www.tjmitchell.com/stuart/dna.html)

DNA structure

DNA structure shows a variety of forms, both double-stranded and single-stranded. The mechanical properties of DNA, which are directly related to its structure, are a significant problem for cells. Every process which binds or reads DNA is able to use or modify the mechanical properties of DNA for purposes of recognition, packaging and modification. The extreme length (a chromosome may contain a 10 cm long DNA strand), relative rigidity and helical structure of DNA has led to the evolution of histones and of enzymes such as topoisomerases and helicases to manage a cell's DNA. The properties of DNA are closely related to its molecular structure and sequence, particularly the weakness of the hydrogen bonds and electronic interactions that hold strands of DNA together compared to the strength of the bonds within each strand.

Experimental techniques which can directly measure the mechanical properties of DNA are relatively new, and high-resolution visualization in solution is often difficult. Nevertheless, scientists have uncovered large amount of data on the mechanical properties of this polymer, and the implications of DNA's mechanical properties on cellular processes is a topic of active current research.

It is important to note the DNA found in many cells can be macroscopic in length - a few centimetres long for each human chromosome. Consequently, cells must compact or "package" DNA to carry it within them. In eukaryotes this is carried by spool-like proteins known as histones, around which DNA winds. It is the further compaction of this DNA-protein complex which produces the well known mitotic eukaryotic chromosomes.

Structure determination

DNA structures can be determined using either nuclear magnetic resonance spectroscopy or X-ray crystallography. The first published reports of A-DNA X-ray diffraction patterns-- and also B-DNA—employed analyses based on Patterson transforms that provided only a limited amount of structural information for oriented fibers of DNA isolated from calf thymus.[1] [2] An alternate analysis was then proposed by Wilkins et al. in 1953 for B-DNA X-ray diffraction/scattering patterns of hydrated, bacterial oriented DNA fibers and trout sperm heads in terms of squares of Bessel functions.[3] Although the `B-DNA form' is most common under the conditions found in cells,[4] it is not a well-defined conformation but a family or fuzzy set of DNA-conformations that occur at the high hydration levels present in a wide variety of living cells.[5] Their corresponding X-ray diffraction & scattering patterns are characteristic of molecular paracrystals with a significant degree of disorder (>20%)[6] [7] , and concomitantly the structure is not tractable using only the standard analysis.

On the other hand, the standard analysis, involving only Fourier transforms of Bessel functions[8] and DNA molecular models, is still routinely employed for the analysis of A-DNA and Z-DNA X-ray diffraction patterns.[9]

Base pair geometry

The geometry of a base, or base pair step can be characterized by 6 coordinates: Shift, Slide, Rise, Tilt, Roll, and Twist. These values precisely define the location and orientation in space of every base or base pair in a DNA molecule relative to its predecessor along the axis of the helix. Together, they characterize the helical structure of the molecule. In regions of DNA where the "normal" structure is disrupted the change in these values can be used to describe such disruption.

For each base pair, considered relative to its predecessor[10] [11] [12] :

Shear

Stretch

Stagger

Buckle

Propeller twist

> Rotation of one base with respect to the other in the same base pair.

Opening

Shift

> displacement along an axis in the base-pair plane perpendicular to the first, directed from the minor to the major groove.

Slide

> displacement along an axis in the plane of the base pair directed from one strand to the other.

Rise

> displacement along the helix axis.

Tilt

> rotation around this axis.

Roll

> rotation around this axis.

Twist

> rotation around the helix axis.

x-displacement

y-displacement

inclination

tip

pitch

> the number of base pairs per complete turn of the helix

Rise and twist determine the handedness and pitch of the helix. The other coordinates, by contrast, can be zero. Slide and shift are typically small in B-DNA, but are substantial in A- and Z-DNA. Roll and tilt make successive base pairs less parallel, and are typically small. A diagram [13] of these coordinates can be found in 3DNA [14] website.

Note that "tilt" has often been used differently in the scientific literature, referring to the deviation of the first, inter-strand base-pair axis from perpendicularity to the helix axis. This

corresponds to slide between a succession of base pairs, and in helix-based coordinates is properly termed "inclination".

DNA helix geometries

Three DNA conformations are believed to be found in nature, A-DNA, B-DNA, and Z-DNA. The "B" form described by James D. Watson and Francis Crick is believed to predominate in cells[15] . It is 23.7 Å wide and extends 34 Å per 10 bp of sequence. The double helix makes one complete turn about its axis every 10.4-10.5 base pairs in solution. This frequency of twist (known as the helical *pitch*) depends largely on stacking forces that each base exerts on its neighbours in the chain.

Other conformations are possible; A-DNA, B-DNA, C-DNA, D-DNA[16] , E-DNA[17] , L-DNA(enantiomeric form of D-DNA)[16] , P-DNA[18] , S-DNA, Z-DNA, etc. have been described so far.[19] In fact, only the letters F, Q, U, V, and Y are now available to describe any new DNA structure that may appear in the future.[20] [21] However, most of these forms have been created synthetically and have not been observed in naturally occurring biological systems. Also note the triple-stranded DNA possibility.

A- and Z-DNA

A-DNA and Z-DNA differ significantly in their geometry and dimensions to B-DNA, although still form helical structures. The A form appears likely to occur only in dehydrated samples of DNA, such as those used in crystallographic experiments, and possibly in hybrid pairings of DNA and RNA strands. Segments of DNA that cells have methylated for regulatory purposes may adopt the Z geometry, in which the strands turn about the helical axis the opposite way to A-DNA and B-DNA. There is also evidence of protein-DNA complexes forming Z-DNA structures.

The structures of A-, B-, and Z-DNA.

The helix axis of A-, B-, and Z-DNA.
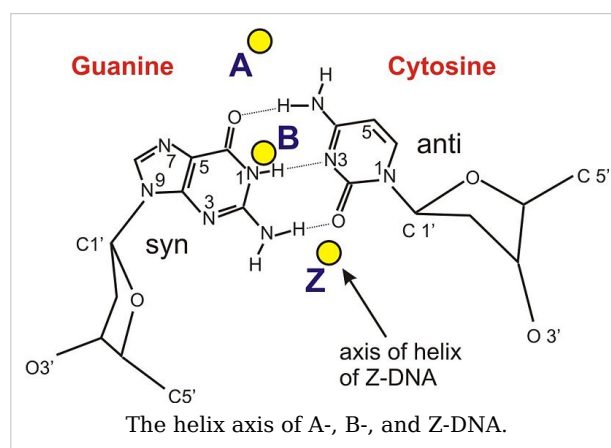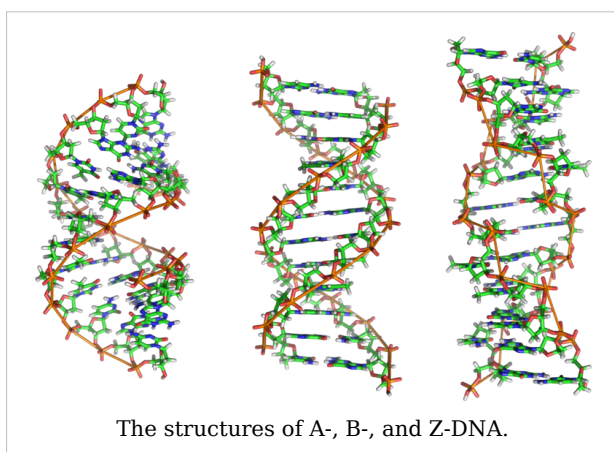
Geometry attribute	A-DNA	B-DNA	Z-DNA
Helix sense	right-handed	right-handed	left-handed
Repeating unit	1 bp	1 bp	2 bp
Rotation/bp	33.6°	35.9°	60°/2bp
Mean bp/turn	10.7	10.0	12
Inclination of bp to axis	+19°	-1.2°	-9°
Rise/bp along axis	2.3 Å	3.32 Å	3.8 Å

Pitch/turn of helix	24.6 Å	33.2 Å	45.6 Å
Mean propeller twist	+18°	+16°	0°
Glycosyl angle	anti	anti	**C**: anti, **G**: syn
Sugar pucker	C3'-endo	C2'-endo	**C**: C2'-endo, **G**: C2'-exo
Diameter	25.5 Å	23.7 Å	18.4 Å

Supercoiled DNA

The B form of the DNA helix twists 360° per 10.4-10.5 bp in the absence of torsional strain. But many molecular biological processes can induce torsional strain. A DNA segment with excess or insufficient helical twisting is referred to, respectively, as positively or negatively "supercoiled". DNA *in vivo* is typically negatively supercoiled, which facilitates the unwinding (melting) of the double-helix required for RNA transcription.

Non-helical forms

Other non-double helical forms of DNA have been described, for example side-by-side (SBS) and triple helical configurations. Single stranded DNA may exist *in statu nascendi* or as thermally induced despiralized DNA.

DNA bending

DNA is a relatively rigid polymer, typically modelled as a worm-like chain. It has three significant degrees of freedom; bending, twisting and compression, each of which cause particular limitations on what is possible with DNA within a cell. Twisting/torsional stiffness is important for the circularisation of DNA and the orientation of DNA bound proteins relative to each other and bending/axial stiffness is important for DNA wrapping and circularisation and protein interactions. Compression/extension is relatively unimportant in the absence of high tension.

Persistence length/Axial stiffness

Example sequences and their persistence lengths (B DNA)

Sequence	Persistence Length /base pairs
Random	154±10
(CA)$_{repeat}$	133±10
(CAG)$_{repeat}$	124±10
(TATA)$_{repeat}$	137±10

DNA in solution does not take a rigid structure but is continually changing conformation due to thermal vibration and collisions with water molecules, which makes classical measures of rigidity impossible. Hence, the bending stiffness of DNA is measured by the persistence length, defined as:

>"The length of DNA over which the time-averaged orientation of the polymer becomes uncorrelated by a factor of *e*."

This value may be directly measured using an atomic force microscope to directly image DNA molecules of various lengths. In aqueous solution the average persistence length is 46-50 nm or 140-150 base pairs (the diameter of DNA is 2 nm), although can vary significantly. This makes DNA a moderately stiff molecule.

The persistence length of a section of DNA is somewhat dependent on its sequence, and this can cause significant variation. The variation is largely due to base stacking energies and the residues which extend into the minor and major grooves.

Models for DNA bending

Stacking stability of base steps (B DNA)

Step	Stacking ΔG /kcal mol^{-1}
T A	-0.19
T G or **C A**	-0.55
C G	-0.91
A G or **C T**	-1.06
A A or **T T**	-1.11
A T	-1.34
G A or **T C**	-1.43
C C or **G G**	-1.44
A C or **G T**	-1.81
G C	-2.17

The entropic flexibility of DNA is remarkably consistent with standard polymer physics models such as the *Kratky-Porod* worm-like chain model. Consistent with the worm-like chain model is the observation that bending DNA is also described by Hooke's law at very small (sub-piconewton) forces. However for DNA segments less than the persistence length, the bending force is approximately constant and behaviour deviates from the worm-like chain predictions.

This effect results in unusual ease in circularising small DNA molecules and a higher probability of finding highly bent sections of DNA.

Bending preference

DNA molecules often have a preferred direction to bend, ie. anisotropic bending. This is, again, due to the properties of the bases which make up the DNA sequence - a random sequence will have no preferred bend direction, i.e. isotropic bending.

Preferred DNA bend direction is determined by the stability of stacking each base on top of the next. If unstable base stacking steps are always found on one side of the DNA helix then the DNA will preferentially bend away from that direction. As bend angle increases then steric hindrances and ability to roll the residues relative to each other also play a role, especially in the minor groove. **A** and **T** residues will be preferentially be found in the minor

grooves on the inside of bends. This effect is particularly seen in DNA-protein binding where tight DNA bending is induced, such as in nucleosome particles. See base step distortions above.

DNA molecules with exceptional bending preference can become intrinsically bent. This was first observed in trypanosomatid kinetoplast DNA. Typical sequences which cause this contain stretches of 4-6 **T** and **A** residues separated by **G** and **C** rich sections which keep the A and T residues in phase with the minor groove on one side of the molecule. For example:

```
 |                   |                  |                      |
                     |                  |
G A T T C C C A A A A A T G T C A A A A A A T A G G C A A A A A A T G C
 C A A A A A A T C C C A A A C
```

The intrinsically bent structure is induced by the 'propeller twist' of base pairs relative to each other allowing unusual bifurcated Hydrogen-bonds between base steps. At higher temperatures this structure, and so the intrinsic bend, is lost.

All DNA which bends anisotropically has, on average, a longer persistence length and greater axial stiffness. This increased rigidity is required to prevent random bending which would make the molecule act isotropically.

DNA circularisation

DNA circularisation depends on both the axial (bending) stiffness and torsional (rotational) stiffness of the molecule. For a DNA molecule to successfully circularise it must be long enough to easily bend into the full circle and must have the correct number of bases so the ends are in the correct rotation to allow bonding to occur. The optimum length for circularisation of DNA is around 400 base pairs (136 nm), with an integral number of turns of the DNA helix, i.e. multiples of 10.4 base pairs. Having a non integral number of turns presents a significant energy barrier for circularisation, for example a 10.4 x 30 = 312 base pair molecule will circularise hundreds of times faster than 10.4 x 30.5 ≈ 317 base pair molecule.

DNA stretching

Longer stretches of DNA are entropically elastic under tension. When DNA is in solution, it undergoes continuous structural variations due to the energy available in the solvent. This is due to the thermal vibration of the molecule combined with continual collisions with water molecules. For entropic reasons, more compact relaxed states are thermally accessible than stretched out states, and so DNA molecules are almost universally found in a tangled relaxed layouts. For this reason, a single molecule of DNA will stretch under a force, straightening it out. Using optical tweezers, the entropic stretching behavior of DNA has been studied and analyzed from a polymer physics perspective, and it has been found that DNA behaves largely like the *Kratky-Porod* worm-like chain model under physiologically accessible energy scales.

Under sufficient tension and positive torque, DNA is thought to undergo a phase transition with the bases splaying outwards and the phosphates moving to the middle. This proposed structure for overstretched DNA has been called "P-form DNA," in honor of Linus Pauling who originally presented it as a possible structure of DNA[18]

The mechanical properties DNA under compression have not been characterized due to experimental difficulties in preventing the polymer from bending under the compressive force.

DNA melting

Melting stability of base steps (B DNA)

Step	Melting ΔG /Kcal mol^{-1}
T A	-0.12
T G or **C A**	-0.78
C G	-1.44
A G or **C T**	-1.29
A A or **T T**	-1.04
A T	-1.27
G A or **T C**	-1.66
C C or **G G**	-1.97
A C or **G T**	-2.04
G C	-2.70

DNA melting is the process by which the interactions between the strands of the double helix are broken, separating the two strands of DNA. These bonds are weak, easily separated by gentle heating, enzymes, or physical force. DNA melting preferentially occurs at certain points in the DNA.[22] **T** and **A** rich sequences are more easily melted than **C** and **G** rich regions. Particular base steps are also susceptible to DNA melting, particularly **T A** and **T G** base steps.[23] These mechanical features are reflected by the use of sequences such as **TATAA** at the start of many genes to assist RNA polymerase in melting the DNA for transcription.

Strand separation by gentle heating, as used in PCR, is simple providing the molecules have fewer than about 10,000 base pairs (10 kilobase pairs, or 10 kbp). The intertwining of the DNA strands makes long segments difficult to separate. The cell avoids this problem by allowing its DNA-melting enzymes (helicases) to work concurrently with topoisomerases, which can chemically cleave the phosphate backbone of one of the strands so that it can swivel around the other. Helicases unwind the strands to facilitate the advance of sequence-reading enzymes such as DNA polymerase.

DNA topology

Within the cell most DNA is topologically restricted. DNA is typically found in closed loops (such as plasmids in prokaryotes) which are topologically closed, or as very long molecules whose diffusion coefficients produce effectively topologically closed domains. Linear sections of DNA are also commonly bound to proteins or physical structures (such as membranes) to form closed topological loops.

Francis Crick was one of the first to propose the importance of linking numbers when considering DNA supercoils. In a paper published in 1976, Crick outlined the problem as follows:

> In considering supercoils formed by closed double-stranded molecules of DNA certain mathematical concepts, such as the linking number and the twist, are needed. The meaning of these for a closed ribbon is explained and also that of the writhing number of a closed curve. Some simple examples are given, some of which may be relevant to the structure of chromatin.[24]

Supercoiled structure of circular DNA molecules with low writhe. Note that the helical nature of the DNA duplex is omitted for clarity.
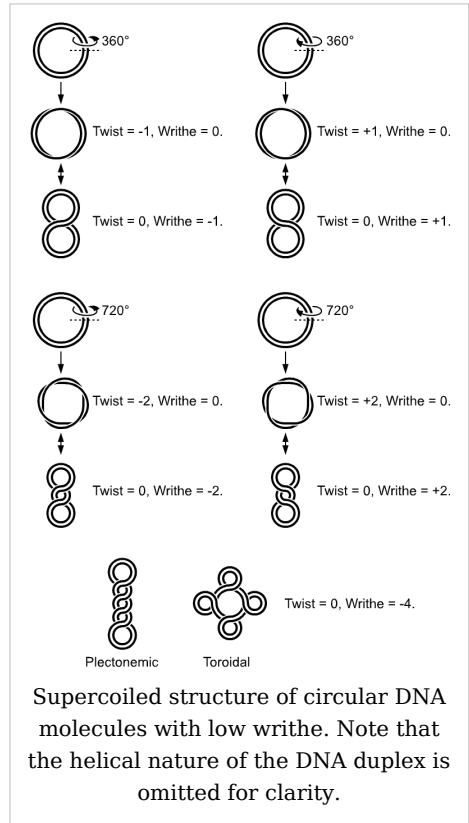
Analysis of DNA topology uses three values:

> L = linking number - the number of times one DNA strand wraps around the other. It is an integer for a closed loop and constant for a closed topological domain.

> T = twist - total number of turns in the double stranded DNA helix. This will normally try to be equal to the number turns a DNA molecule will make while free in solution, ie. number of bases/10.4.

> W = writhe - number of turns of the double stranded DNA helix around the superhelical axis

> $L = T + W$ and $\Delta L = \Delta T + \Delta W$

Any change of T in a closed topological domain must be balanced by a change in W, and vice versa. This results in higher order structure of DNA. A circular DNA molecule with a writhe of 0 will be circular. If the twist of this molecule is subsequently increased or decreased by supercoiling then the writhe will be appropriately altered, making the molecule undergo plectonemic or toroidal superhelical coiling.

When the ends of a piece of double stranded helical DNA are joined so that it forms a circle the strands are topologically knotted. This means the single strands cannot be separated any process that does not involve breaking a strand (such as heating). The task of un-knotting topologically linked strands of DNA falls to enzymes known as topoisomerases. These enzymes are dedicated to un-knotting circular DNA by cleaving one or both strands so that another double or single stranded segment can pass through. This un-knotting is required for the replication of circular DNA and various types of recombination in linear DNA which have similar topological constraints.

The linking number paradox

For many years, the origin of residual supercoiling in eukaryotic genomes remained unclear. This topological puzzle was referred to by some as the "linking number paradox".[25] However, when experimentally determined structures of the nucleosome displayed an overtwisted left-handed wrap of DNA around the histone octamer[26] [27] , this "paradox" was solved.

See also

- DNA nanotechnology
- Molecular models of DNA

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External links

- MDDNA: Structural Bioinformatics of DNA (http://humphry.chem.wesleyan.edu:8080/MDDNA/)
- Ascalaph DNA (http://www.agilemolecule.com/Ascalaph/Ascalaph_DNA.html) — Commercial software for DNA modeling
- DNAlive: a web interface to compute DNA physical properties (http://mmb.pcb.ub.es/DNAlive). Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- DiProDB: Dinucleotide Property Database (http://diprodb.fli-leibniz.de). The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.

Paracrystalline

Paracrystalline materials are defined as having short and medium range ordering in their lattice (similar to the liquid crystal phases) but lacking long-range ordering at least in one direction.[1]

Ordering is the regularity in which atoms appear in a predictable lattice, as measured from one point. In a highly ordered, perfectly crystalline material, or single crystal, the location of every atom in the structure can be described exactly measuring out from a single origin. Conversely, in a disordered structure such as a liquid or amorphous solid, the location of the first and perhaps second nearest neighbors can be described from an origin (with some degree of uncertainty) and the ability to predict locations decreases rapidly from there out. The distance at which atom locations can be predicted is referred to as the correlation length ξ. A paracrystalline material exhibits correlation somewhere between the fully amorphous and fully crystalline.

The primary, most accessible source of crystallinity information is X-ray diffraction, although other techniques may be needed to observe the complex structure of paracrystalline materials, such as fluctuation electron microscopy [2] in combination with Density of states modeling[3] of electronic and vibrational states.

Paracrystalline Model

The paracrystalline model is a revision of the Continuous Random Network model first proposed by W. H. Zachariasen in 1932 [4] . The paracrystal model is defined as highly strained, microcrystalline grains surrounded by fully amorphous material [5] . This is a higher energy state then the continuous random network model. The important distinction between this model and the microcrystalline phases is the lack of defined grain boundaries and highly strained lattice parameters, which makes calculations of molecular and lattice dynamics difficult. A general theory of paracrystals has been formulated in a basic textbook[6] , and then further developed/refined by various authors.

Applications

The paracrystal model has been useful, for example, in describing the state of partially amorphous semiconductor materials after deposition. It has also been successfully applied to: synthetic polymers, liquid crystals, biopolymers [7] ,[8] and biomembranes[9] .

See also

- X-ray scattering
- Amorphous solid
- Single Crystal
- Polycrystalline
- Crystallography
- DNA
- X-ray pattern of a B-DNA Paracrystal [10]

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DNA Dynamics

DNA Molecular dynamics modeling involves simulations of DNA molecular geometry and topology changes with time as a result of both intra- and inter- molecular interactions of DNA. Whereas molecular models of Deoxyribonucleic acid (DNA) molecules such as closely packed spheres (CPK models) made of plastic or metal wires for 'skeletal models' are useful representations of static DNA structures, their usefulness is very limited for representing complex DNA dynamics. Computer molecular modeling allows both animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*.

An old standing dynamic problem is how DNA "self-replication" takes place in living cells that should involve transient uncoiling of supercoiled DNA fibers. Although DNA consists of relatively rigid, very large elongated biopolymer molecules called "fibers" or chains its molecular structure *in vivo* undergoes dynamic configuration changes that involve dynamically attached water molecules, ions or proteins/enzymes. Supercoiling, packing with histones in chromosome structures, and other such supramolecular aspects also involve *in vivo* DNA topology which is even more complex than DNA molecular geometry, thus turning molecular modeling of DNA dynamics into a series of challenging problems for biophysical chemists, molecular biologists and biotechnologists. Thus, DNA exists in multiple stable geometries (called conformational isomerism) and has a rather large number of configurational, quantum states which are close to each other in energy on the potential energy surface of the DNA molecule.

Such varying molecular geometries can also be computed, at least in principle, by employing *ab initio* quantum chemistry methods that can attain high accuracy for small molecules, although claims that acceptable accuracy can be also achieved for polynuclelotides, as well as DNA conformations, were recently made on the basis of VCD spectral data. Such quantum geometries define an important class of *ab initio* molecular models of DNA whose exploration has barely started especially in connection with results obtained by VCD in solutions. More detailed comparisons with such *ab initio* quantum computations are in principle obtainable through 2D-FT NMR spectroscopy and relaxation studies of polynucleotide solutions or specifically labeled DNA, as for example with

deuterium labels.

Importance of DNA molecular structure and dynamics modeling for Genomics and beyond

From the very early stages of structural studies of DNA by X-ray diffraction and biochemical means, molecular models such as the Watson-Crick double-helix model were successfully employed to solve the 'puzzle' of DNA structure, and also find how the latter relates to its key functions in living cells. The first high quality X-ray diffraction patterns of A-DNA were reported by Rosalind Franklin and Raymond Gosling in 1953[1] . The first reports of a double-helix molecular model of B-DNA structure were made by Watson and Crick in 1953[2] [3] . Then Maurice F. Wilkins, A. Stokes and H.R. Wilson, reported the first X-ray patterns of *in vivo* B-DNA in partially oriented salmon sperm heads [4] . The development of the first correct double-helix molecular model of DNA by Crick and Watson may not have been possible without the biochemical evidence for the nucleotide base-pairing ([A---T]; [C---G]), or Chargaff's rules[5] [6] [7] [8] [9] [10] . Although such initial studies of DNA structures with the help of molecular models were essentially static, their consequences for explaining the *in vivo* functions of DNA were significant in the areas of protein biosynthesis and the quasi-universality of the genetic code. Epigenetic transformation studies of DNA *in vivo* were however much slower to develop in spite of their importance for embryology, morphogenesis and cancer research. Such chemical dynamics and biochemical reactions of DNA are much more complex than the molecular dynamics of DNA physical interactions with water, ions and proteins/enzymes in living cells.

Animated DNA molecular models and hydrogen-bonding

Animated molecular models allow one to visually explore the three-dimensional (3D) structure of DNA. The first DNA model is a space-filling, or CPK, model of the DNA double-helix whereas the third is an animated wire, or skeletal type, molecular model of DNA. The last two DNA molecular models in this series depict quadruplex DNA [13] that may be involved in certain cancers[11] [12] . The first CPK model in the second row is a molecular model of hydrogen bonds between water molecules in ice that are broadly similar to those found in DNA; the hydrogen bonding dynamics and proton exchange is however very different by many orders of magnitude between the two systems of fully hydrated DNA and water molecules in ice. Thus, the DNA dynamics is complex, involving nanosecond and several tens of picosecond time scales, whereas that of liquid ice is on the picosecond time scale, and that of proton exchange in ice is on the millisecond time scale; the proton exchange rates in DNA and attached proteins may vary from picosecond to nanosecond, minutes or years, depending on the exact locations of the exchanged protons in the large biopolymers. The simple harmonic oscillator 'vibration' in the third, animated image of the next gallery is only an oversimplified dynamic representation of the longitudinal vibrations of the DNA intertwined helices which were found to be anharmonic rather than harmonic as often assumed in quantum dynamic simulations of DNA.
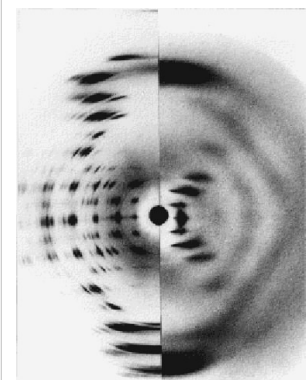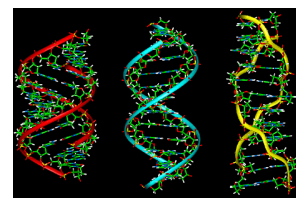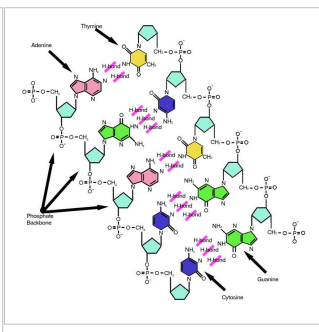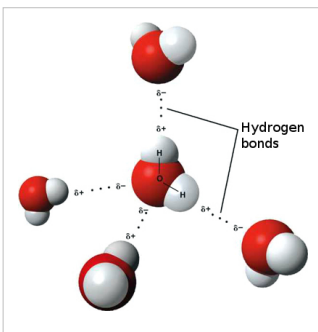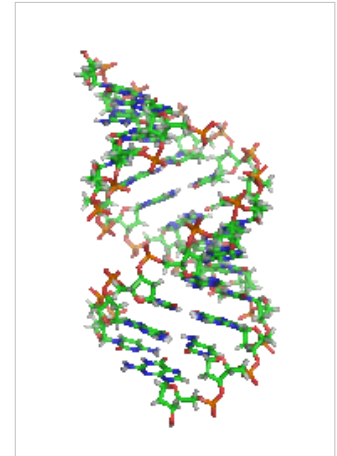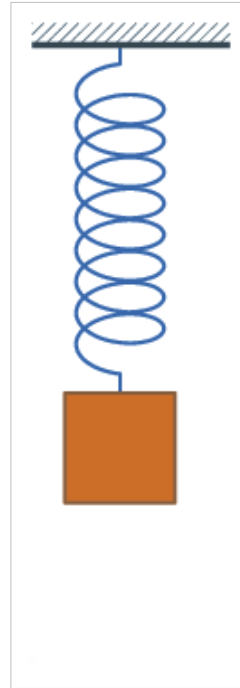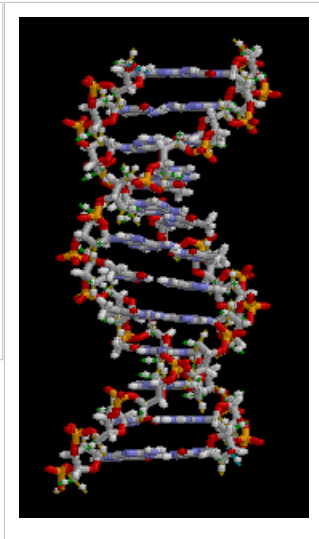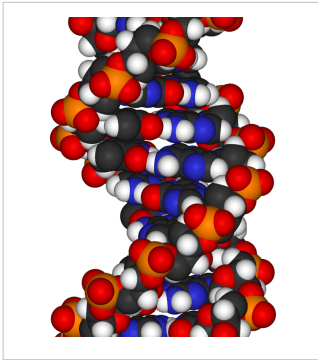
A-DNA   B-DNA
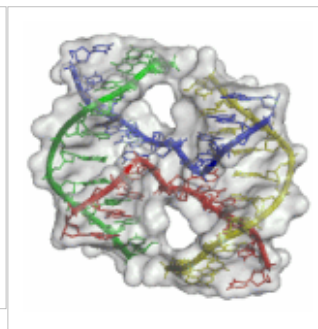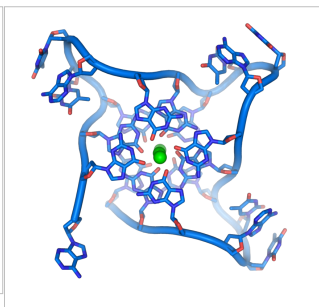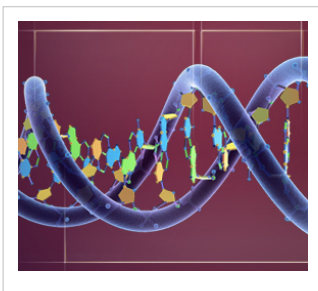
Human Genomics and Biotechnology Applications of DNA Molecular Modeling

The following two galleries of images illustrate various uses of DNA molecular modeling in Genomics and Biotechnology research applications from DNA repair to PCR and DNA nanostructures; each slide contains its own explanation and/or details. The first slide presents an overview of DNA applications, including DNA molecular models, with emphasis on Genomics and Biotechnology.

Applications of DNA molecular dynamics computations

- *First row* images present a DNA biochip and DNA nanostructures designed for DNA computing and other dynamic applications of DNA nanotechnology; last image in this row is of DNA arrays that display a representation of the Sierpinski gasket on their surfaces.
- *Second row*: the first two images show computer molecular models of RNA polymerase, followed by that of an E. coli, bacterial DNA primase template suggesting very complex dynamics at the interfaces between the enzymes and the DNA template; the fourth image illustrates in a computed molecular model the mutagenic, chemical interaction of a potent carcinogen molecule with DNA, and the last image shows the different interactions of specific fluorescence labels with DNA in human and orangoutan chromosomes.
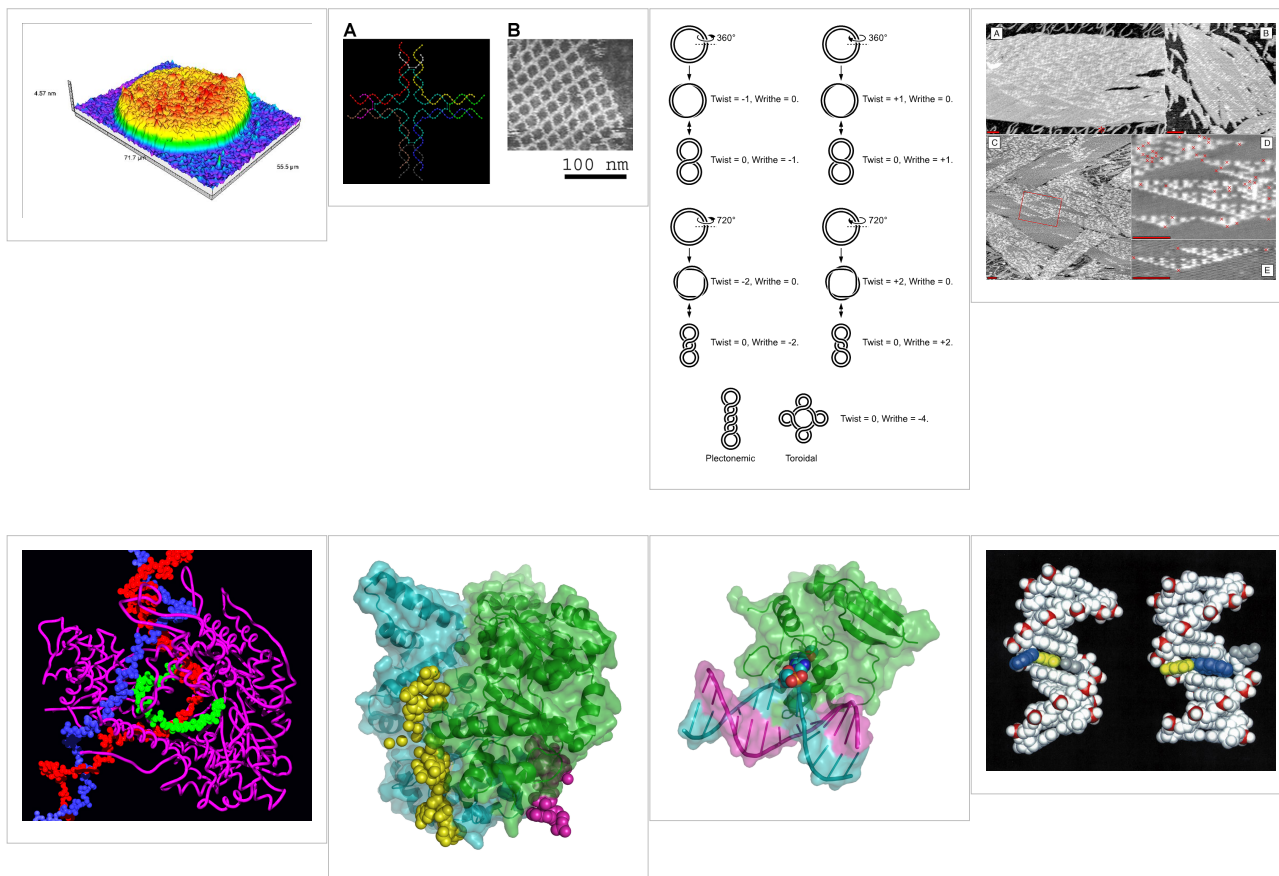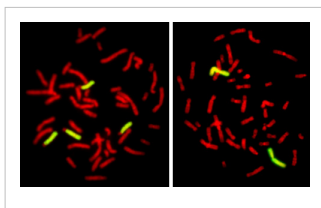
Image Gallery: *DNA Applications and Technologies at various scales in Biotechnology and Genomics research*

The first figure is an actual electron micrograph of a DNA fiber bundle, presumably of a single plasmid, bacterial DNA loop.
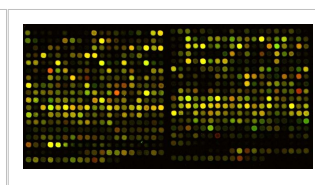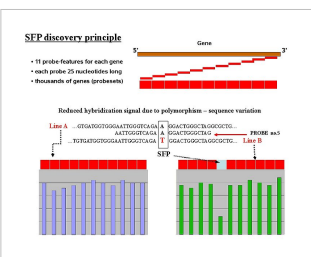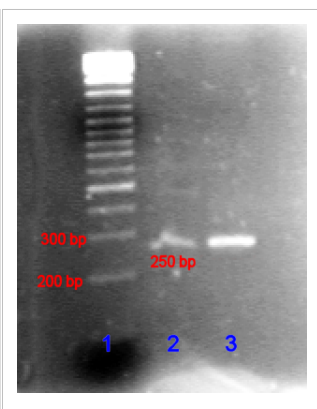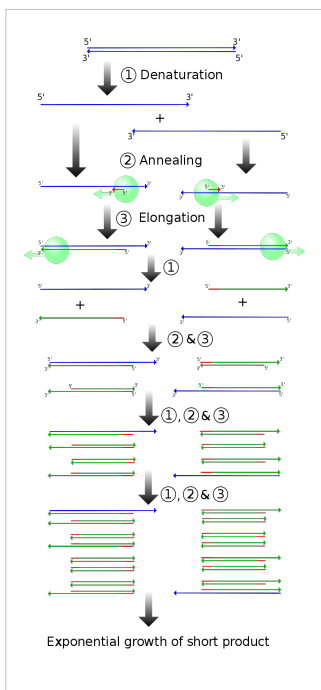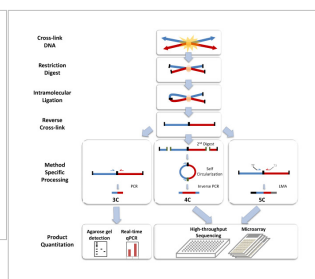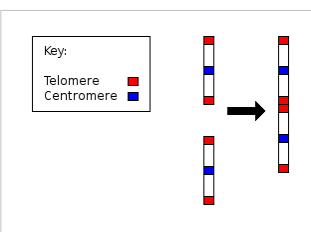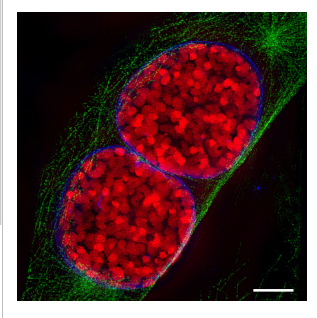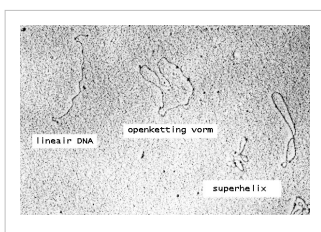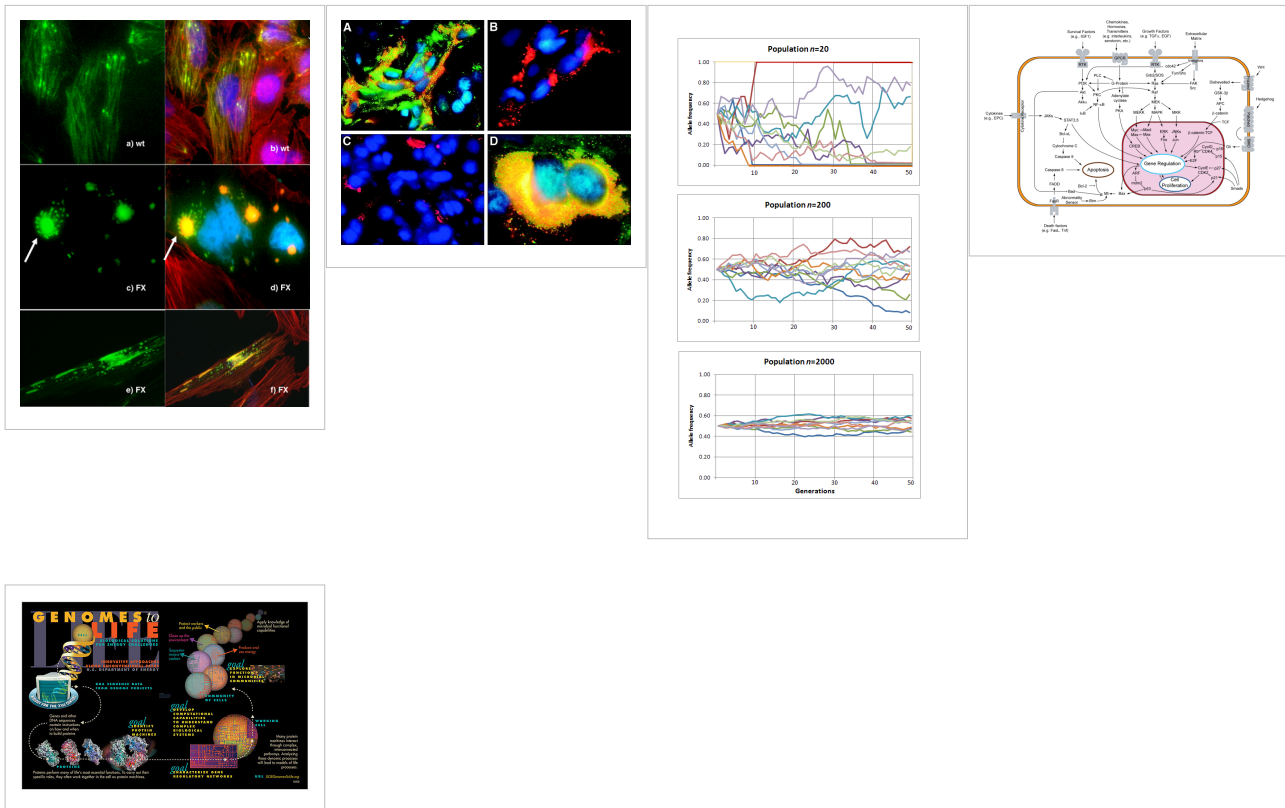
Databases for Genomics, DNA Dynamics and Sequencing

Genomic and structural databases

- CBS Genome Atlas Database [57] — contains examples of base skews.[13]
- The Z curve database of genomes — a 3-dimensional visualization and analysis tool of genomes [59][14] .
- DNA and other nucleic acids' molecular models: Coordinate files of nucleic acids molecular structure models in PDB and CIF formats [61]

Mass spectrometry--Maldi informatics
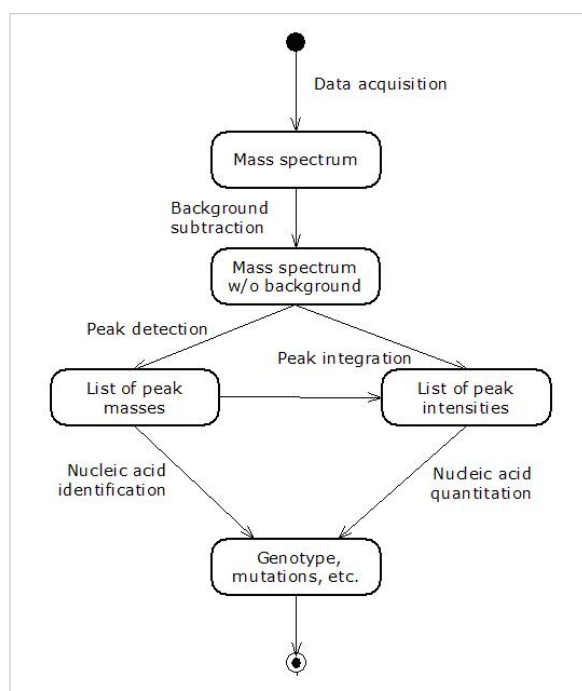
DNA Dynamics Data from Spectroscopy

- FT-NMR[15] [16]
  - NMR Atlas--database [29]
  - mmcif downloadable coordinate files of nucleic acids in solution from 2D-FT NMR data [30]
  - NMR constraints files for NAs in PDB format [31]
- NMR microscopy[17]
- Vibrational circular dichroism (VCD)
- Microwave spectroscopy
- FT-IR
- FT-NIR[18] [19] [20]
- Spectral, Hyperspectral, and Chemical imaging)[21] [22] [23] [24] [25] [26] [27] .
- Raman spectroscopy/microscopy[28] and CARS[29] .
- Fluorescence correlation spectroscopy[30] [31] [32] [33] [34] [35] [36] [37] , Fluorescence cross-correlation spectroscopy and FRET[38] [39] [40] .
- Confocal microscopy[41]

Gallery: CARS (Raman spectroscopy), Fluorescence confocal microscopy, and Hyperspectral imaging
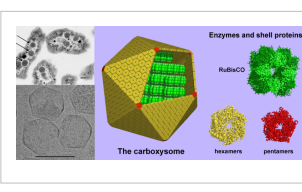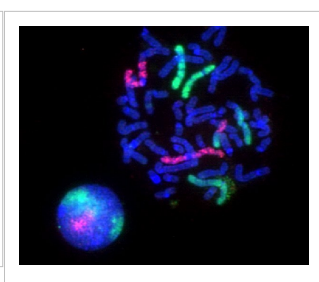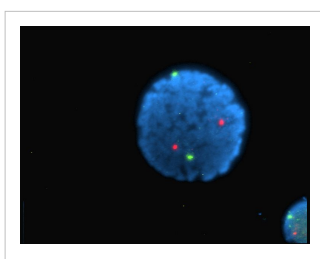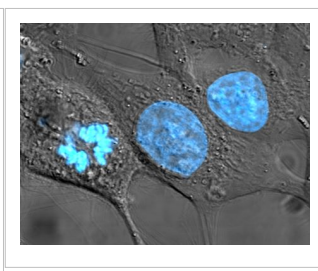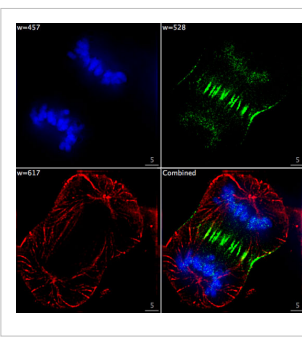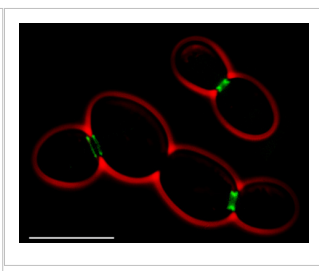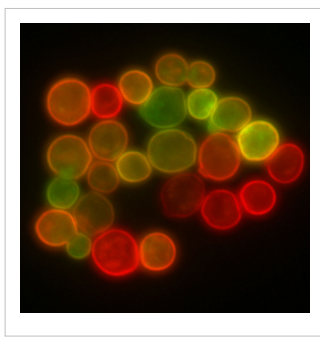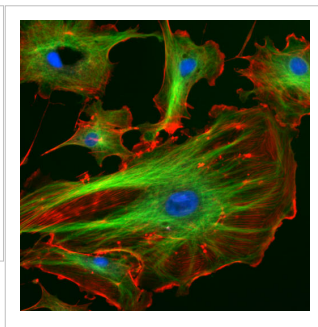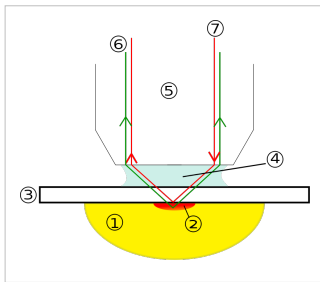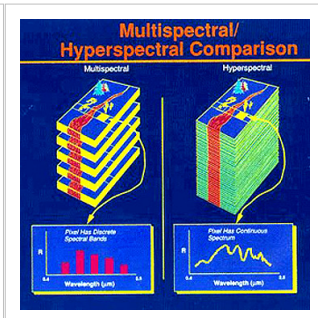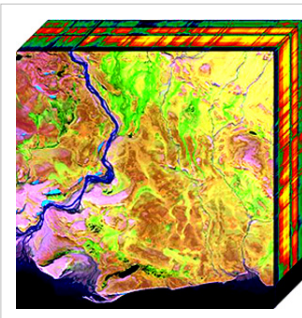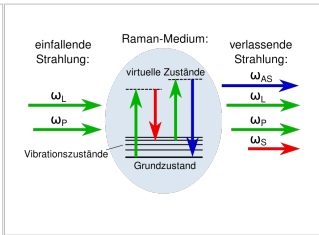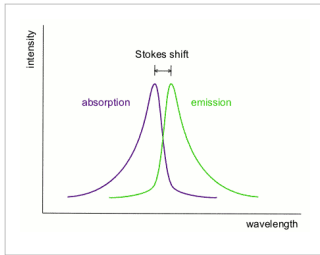
X-ray microscopy

- Application of X-ray microscopy in the analysis of living hydrated cells [18]

Atomic Force Microscopy (AFM)

Two-dimensional DNA junction arrays have been visualized by Atomic Force Microscopy (AFM)[42] . Other imaging resources for AFM/Scanning probe microscopy(SPM) can be freely accessed at:

- How SPM Works [25]
- SPM Image Gallery - AFM STM SEM MFM NSOM and more. [26]

Gallery of AFM Images of DNA Nanostructures
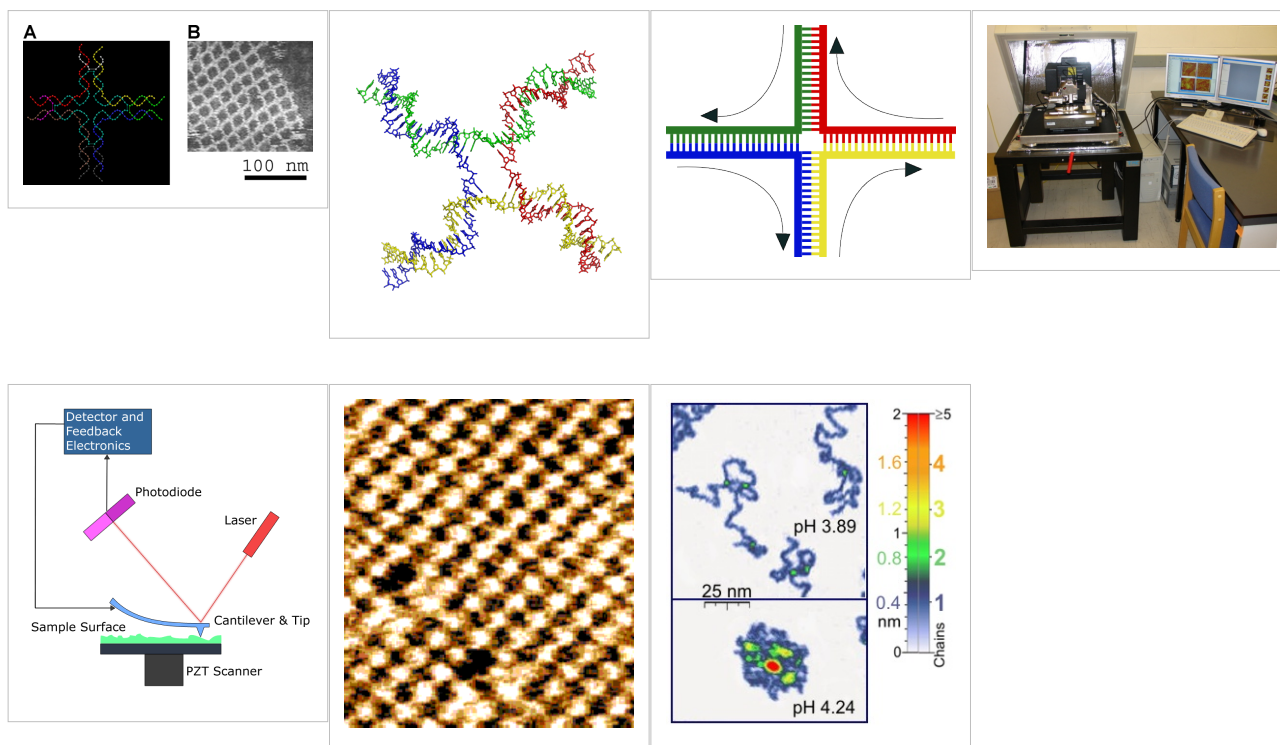
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See also

- DNA
- Molecular modeling of DNA
- Genomics
- Signal transduction
- Transcriptomics
- Interactomics
- Biotechnology
- Molecular graphics
- Quantum computing
- MAYA-II
- DNA computing
- DNA structure
- Molecular structure
- Molecular dynamics
- Molecular topology
- DNA topology
- DNA, the Genome and Interactome
- Molecular structure
- Molecular geometry fluctuations
- Molecular interactions
- Molecular topology
- Hydrogen bonding
- Hydrophobic interactions
- DNA dynamics and conformations
- DNA Conformational isomerism
- 2D-FT NMRI and Spectroscopy
- Paracrystalline lattices/Paracrystals
- NMR Spectroscopy
- VCD or Vibrational circular dichroism
- Microwave spectroscopy
- Two-dimensional IR spectroscopy
- FRET and FCS- Fluorescence correlation spectroscopy
- Fluorescence cross-correlation spectroscopy (FCCS)
- Spectral imaging
- Hyperspectral imaging
- Chemical imaging
- NMR microscopy
- X-ray scattering
- Neutron scattering
- Crystallography
- Crystal lattices
- Molecular geometry
- Nanostructure
- DNA nanotechnology
- Imaging
- Sirius visualization software

- Atomic force microscopy
- X-ray microscopy
- Liquid crystals
- Glasses
- QMC@Home
- Sir Lawrence Bragg, FRS
- Sir John Randall
- Francis Crick
- Manfred Eigen
- Felix Bloch
- Paul Lauterbur
- Maurice Wilkins
- Herbert Wilson, FRS
- Alex Stokes

External links

- DNAlive: a web interface to compute DNA physical properties (http://mmb.pcb.ub.es/ DNAlive). Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- Application of X-ray microscopy in analysis of living hydrated cells (http://www.ncbi. nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract& list_uids=12379938)
- DiProDB: Dinucleotide Property Database (http://diprodb.fli-leibniz.de). The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.
- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/ dna_double_helix/) From the official Nobel Prize web site
- MDDNA: Structural Bioinformatics of DNA (http://humphry.chem.wesleyan.edu:8080/ MDDNA/)
- Double Helix 1953–2003 (http://www.ncbe.reading.ac.uk/DNA50/) National Centre for Biotechnology Education
- DNA under electron microscope (http://www.fidelitysystems.com/Unlinked_DNA. html)
- Further details of mathematical and molecular analysis of DNA structure based on X-ray data (http://planetphysics.org/encyclopedia/ BesselFunctionsApplicationsToDiffractionByHelicalStructures.html)
- Bessel functions corresponding to Fourier transforms of atomic or molecular helices. (http://planetphysics.org/?op=getobj&from=objects& name=BesselFunctionsAndTheirApplicationsToDiffractionByHelicalStructures)
- Characterization in nanotechnology some pdfs (http://nanocharacterization.sitesled. com/)
- An overview of STM/AFM/SNOM principles with educative videos (http://www.ntmdt. ru/SPM-Techniques/Principles/)
- SPM Image Gallery - AFM STM SEM MFM NSOM and More (http://www.rhk-tech.com/ results/showcase.php)
- How SPM Works (http://www.parkafm.com/New_html/resources/01general.php)

- U.S. National DNA Day (http://www.genome.gov/10506367) — watch videos and participate in real-time discussions with scientists.
- The Secret Life of DNA - DNA Music compositions (http://www.tjmitchell.com/stuart/dna.html)
- Ascalaph DNA (http://www.agilemolecule.com/Ascalaph/Ascalaph_DNA.html) — Commercial software for DNA modeling

Genomics

Genomics is the study of the genomes of organisms. The field includes intensive efforts to determine the entire DNA sequence of organisms and fine-scale genetic mapping efforts. The field also includes studies of intragenomic phenomena such as heterosis, epistasis, pleiotropy and other interactions between loci and alleles within the genome. In contrast, the investigation of the roles and functions of single genes is a primary focus of molecular biology and is a common topic of modern medical and biological research. Research of single genes does not fall into the definition of genomics unless the aim of this genetic, pathway, and functional information analysis is to elucidate its effect on, place in, and response to the entire genome's networks.

For the United States Environmental Protection Agency, "the term "genomics" encompasses a broader scope of scientific inquiry associated technologies than when genomics was initially considered. A genome is the sum total of all an individual organism's genes. Thus, genomics is the study of all the genes of a cell, or tissue, at the DNA (genotype), mRNA (transcriptome), or protein (proteome) levels."[1]

History

Genomics was established by Fred Sanger when he first sequenced the complete genomes of a virus and a mitochondrion. His group established techniques of sequencing, genome mapping, data storage, and bioinformatic analyses in the 1970-1980s. A major branch of genomics is still concerned with sequencing the genomes of various organisms, but the knowledge of full genomes has created the possibility for the field of functional genomics, mainly concerned with patterns of gene expression during various conditions. The most important tools here are microarrays and bioinformatics. Study of the full set of proteins in a cell type or tissue, and the changes during various conditions, is called proteomics. A related concept is materiomics, which is defined as the study of the material properties of biological materials (e.g. hierarchical protein structures and materials, mineralized biological tissues, etc.) and their effect on the macroscopic function and failure in their biological context, linking processes, structure and properties at multiple scales through a materials science approach. The actual term 'genomics' is thought to have been coined by Dr. Tom Roderick, a geneticist at the Jackson Laboratory (Bar Harbor, ME) over beer at a meeting held in Maryland on the mapping of the human genome in 1986.

In 1972, Walter Fiers and his team at the Laboratory of Molecular Biology of the University of Ghent (Ghent, Belgium) were the first to determine the sequence of a gene: the gene for Bacteriophage MS2 coat protein.[2] In 1976, the team determined the complete nucleotide-sequence of bacteriophage MS2-RNA.[3] The first DNA-based genome to be sequenced in its entirety was that of bacteriophage Φ-X174; (5,368 bp), sequenced by

Frederick Sanger in 1977.[4]

The first free-living organism to be sequenced was that of *Haemophilus influenzae* (1.8 Mb) in 1995, and since then genomes are being sequenced at a rapid pace. A rough draft of the human genome was completed by the Human Genome Project in early 2001, creating much fanfare.

As of September 2007, the complete sequence was known of about 1879 viruses [5] , 577 bacterial species and roughly 23 eukaryote organisms, of which about half are fungi. [6] Most of the bacteria whose genomes have been completely sequenced are problematic disease-causing agents, such as *Haemophilus influenzae*. Of the other sequenced species, most were chosen because they were well-studied model organisms or promised to become good models. Yeast (*Saccharomyces cerevisiae*) has long been an important model organism for the eukaryotic cell, while the fruit fly *Drosophila melanogaster* has been a very important tool (notably in early pre-molecular genetics). The worm *Caenorhabditis elegans* is an often used simple model for multicellular organisms. The zebrafish *Brachydanio rerio* is used for many developmental studies on the molecular level and the flower *Arabidopsis thaliana* is a model organism for flowering plants. The Japanese pufferfish (*Takifugu rubripes*) and the spotted green pufferfish (*Tetraodon nigroviridis*) are interesting because of their small and compact genomes, containing very little non-coding DNA compared to most species. [7] [8] The mammals dog (*Canis familiaris*), [9] brown rat (*Rattus norvegicus*), mouse (*Mus musculus*), and chimpanzee (*Pan troglodytes*) are all important model animals in medical research.

Bacteriophage genomics

Bacteriophages have played and continue to play a key role in bacterial genetics and molecular biology. Historically, they were used to define gene structure and gene regulation. Also the first genome to be sequenced was a bacteriophage. However, bacteriophage research did not lead the genomics revolution, which is clearly dominated by bacterial genomics. Only very recently has the study of bacteriophage genomes become prominent, thereby enabling researchers to understand the mechanisms underlying phage evolution. Bacteriophage genome sequences can be obtained through direct sequencing of isolated bacteriophages, but can also be derived as part of microbial genomes. Analysis of bacterial genomes has shown that a substantial amount of microbial DNA consists of prophage sequences and prophage-like elements. A detailed database mining of these sequences offers insights into the role of prophages in shaping the bacterial genome.[10]

Cyanobacteria genomics

At present there are 24 cyanobacteria for which a total genome sequence is available. 15 of these cyanobacteria come from the marine environment. These are six *Prochlorococcus* strains, seven marine *Synechococcus* strains, *Trichodesmium erythraeum* IMS101 and *Crocosphaera watsonii* WH8501. Several studies have demonstrated how these sequences could be used very successfully to infer important ecological and physiological characteristics of marine cyanobacteria. However, there are many more genome projects currently in progress, amongst those there are further *Prochlorococcus* and marine *Synechococcus* isolates, *Acaryochloris* and *Prochloron*, the N_2-fixing filamentous cyanobacteria *Nodularia spumigena*, *Lyngbya aestuarii* and *Lyngbya majuscula*, as well as bacteriophages infecting marine cyanobaceria. Thus, the growing body of genome

information can also be tapped in a more general way to address global problems by applying a comparative approach. Some new and exciting examples of progress in this field are the identification of genes for regulatory RNAs, insights into the evolutionary origin of photosynthesis, or estimation of the contribution of horizontal gene transfer to the genomes that have been analyzed.[11]

See also

- Full Genome Sequencing
- Computational genomics
- Nitrogenomics
- Metagenomics
- Predictive Medicine
- Personal genomics

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External links

- Genomics Directory (http://www.genomicsdirectory.com): A one-stop biotechnology resource center for bioentrepreneurs, scientists, and students
- Annual Review of Genomics and Human Genetics (http://arjournals.annualreviews.org/loi/genom/)
- BMC Genomics (http://www.biomedcentral.com/bmcgenomics/): A BMC journal on Genomics
- Genomics (http://www.genomics.co.uk/companylist.php): UK companies and laboratories* Genomics journal (http://www.elsevier.com/wps/find/journaldescription.cws_home/622838/description#description)
- Genomics.org (http://genomics.org): An openfree wiki based Genomics portal
- NHGRI (http://www.genome.gov/): US government's genome institute
- Pharmacogenomics in Drug Discovery and Development (http://www.springer.com/humana+press/pharmacology+and+toxicology/book/978-1-58829-887-4), a book on pharmacogenomics, diseases, personalized medicine, and therapeutics
- Tishchenko P. D. Genomics: New Science in the New Cultural Situation (http://www.zpu-journal.ru/en/articles/detail.php?ID=342)
- Undergraduate program on Genomic Sciences (spanish) (http://www.lcg.unam.mx/): One of the first undergraduate programs in the world
- JCVI Comprehensive Microbial Resource (http://cmr.jcvi.org/)
- Pathema: A Clade Specific Bioinformatics Resource Center (http://pathema.jcvi.org/)
- KoreaGenome.org (http://koreagenome.org): The first Korean Genome published and the sequence is available freely.
- GenomicsNetwork (http://genomicsnetwork.ac.uk): Looks at the development and use of the science and technologies of genomics.

Gene regulatory network

A **gene regulatory network** or **genetic regulatory network (GRN)** is a collection of DNA segments in a cell which interact with each other (indirectly through their RNA and protein expression products) and with other substances in the cell, thereby governing the rates at which genes in the network are transcribed into mRNA. In general, each mRNA molecule goes on to make a specific protein (or set of proteins). In some cases this protein will be structural, and will accumulate at the cell-wall or within the cell to give it particular structural properties. In other cases the protein will be an enzyme; a micro-machine that catalyses a certain reaction, such as the breakdown of a food source or toxin. Some proteins though serve only to activate other genes, and these are the transcription factors that are the main players in regulatory networks or cascades. By

Structure of a Gene Regulatory Network.

Control process of a Gene Regulatory Network.

binding to the promoter region at the start of other genes they turn them on, initiating the production of another protein, and so on. Some transcription factors are inhibitory.

In single-celled organisms regulatory networks respond to the external environment, optimising the cell at a given time for survival in this environment. Thus a yeast cell, finding itself in a sugar solution, will turn on genes to make enzymes that process the sugar to alcohol.[1] This process, which we associate with wine-making, is how the yeast cell makes its living, gaining energy to multiply, which under normal circumstances would enhance its survival prospects.

In multicellular animals the same principle has been put in the service of gene cascades that control body-shape.[2] Each time a cell divides, two cells result which, although they contain the same genome in full, can differ in which genes are turned on and making proteins. Sometimes a 'self-sustaining feedback loop' ensures that a cell maintains its
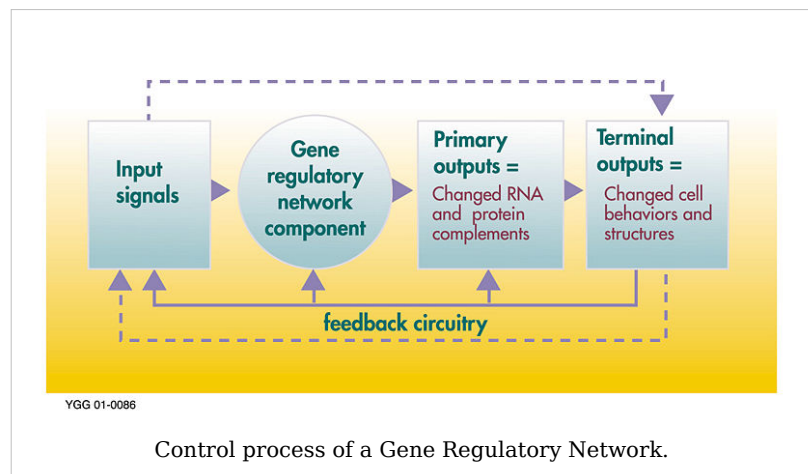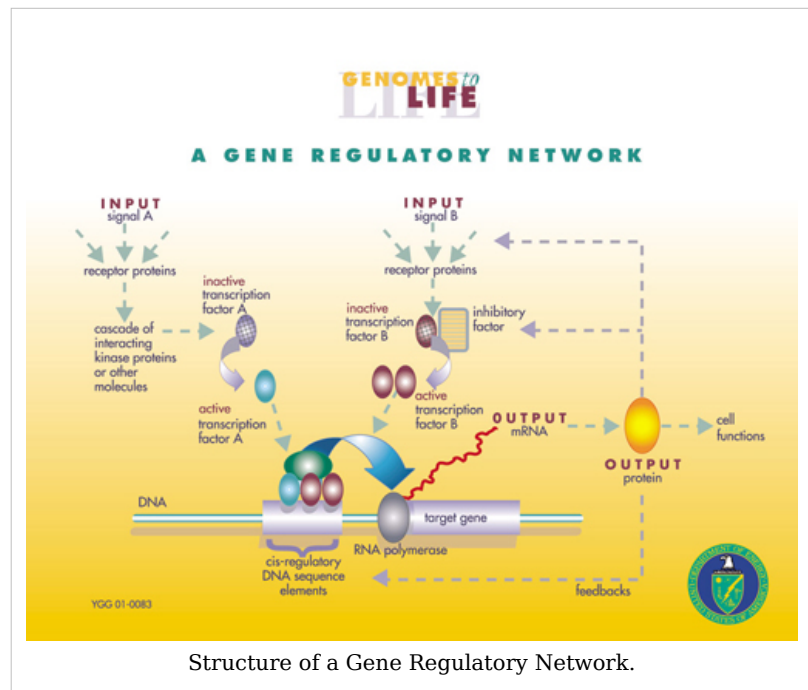
identity and passes it on. Less understood is the mechanism of epigenetics by which chromatin modification may provide cellular memory by blocking or allowing transcription. A major feature of multicellular animals is the use of morphogen gradients, which in effect provide a positioning system that tells a cell where in the body it is, and hence what sort of cell to become. A gene that is turned on in one cell may make a product that leaves the cell and diffuses through adjacent cells, entering them and turning on genes only when it is present above a certain threshold level. These cells are thus induced into a new fate, and may even generate other morphogens that signal back to the original cell. Over longer distances morphogens may use the active process of signal transduction. Such signalling controls embryogenesis, the building of a body plan from scratch through a series of sequential steps. They also control maintain adult bodies through feedback processes, and the loss of such feedback because of a mutation can be responsible for the cell proliferation that is seen in cancer. In parallel with this process of building structure, the gene cascade turns on genes that make structural proteins that give each cell the physical properties it needs.

Overview

At one level, biological cells can be thought of as "partially-mixed bags" of biological chemicals – in the discussion of gene regulatory networks, these chemicals are mostly the mRNAs and proteins that arise from gene expression. These mRNA and proteins interact with each other with various degrees of specificity. Some diffuse around the cell. Others are bound to cell membranes, interacting with molecules in the environment. Still others pass through cell membranes and mediate long range signals to other cells in a multi-cellular organism. These molecules and their interactions comprise a *gene regulatory network*. A typical gene regulatory network looks something like this:

The nodes of this network are proteins, their corresponding mRNAs, and protein/protein complexes. Nodes that are depicted as lying along vertical lines are associated with the cell/environment interfaces, while the others are free-floating and diffusible. Implied are genes, the DNA sequences which are transcribed into the mRNAs that translate into proteins. Edges between nodes represent individual molecular reactions, the protein/protein and protein/mRNA interactions through which the products of one gene affect those of another, though the lack of experimentally obtained information often implies that some reactions are not modeled at such a fine level of detail. These interactions can be inductive (the arrowheads), with an increase in the concentration of one leading to an increase in the other, or inhibitory (the filled circles), with an increase in one leading to a decrease in the other. A series of edges indicates a chain of such dependences, with cycles corresponding to feedback loops. The network structure is an abstraction of the system's chemical dynamics, describing the manifold ways in which one substance affects all the others to which it is connected. In practice, such GRNs are inferred from the biological literature on a given system and represent a distillation of the collective knowledge about a set of related biochemical reactions.

Genes can be viewed as nodes in the network, with input being proteins such as transcription factors, and outputs being the level of gene expression. The node itself can also be viewed as a function which can be obtained by combining basic functions upon the inputs (in the Boolean network described below these are Boolean functions, typically AND, OR, and NOT). These functions have been interpreted as performing a kind of information

processing within the cell, which determines cellular behavior. The basic drivers within cells are concentrations of some proteins, which determine both spatial (location within the cell or tissue) and temporal (cell cycle or developmental stage) coordinates of the cell, as a kind of "cellular memory". The gene networks are only beginning to be understood, and it is a next step for biology to attempt to deduce the functions for each gene "node", to help understand the behavior of the system in increasing levels of complexity, from gene to signaling pathway, cell or tissue level (see systems biology).

Mathematical models of GRNs have been developed to capture the behavior of the system being modeled, and in some cases generate predictions corresponding with experimental observations. In some other cases, models have proven to make accurate novel predictions, which can be tested experimentally, thus suggesting new approaches to explore in an experiment that sometimes wouldn't be considered in the design of the protocol of an experimental laboratory. The most common modeling technique involves the use of coupled ordinary differential equations (ODEs). Several other promising modeling techniques have been used, including Boolean networks, Petri nets, Bayesian networks, graphical Gaussian models, Stochastic, and Process Calculi. Conversely, techniques have been proposed for generating models of GRNs that best explain a set of time series observations.

Modelling

Coupled ODEs

It is common to model such a network with a set of coupled ordinary differential equations (ODEs) or stochastic ODEs, describing the reaction kinetics of the constituent parts. Suppose that our regulatory network has N nodes, and let $S_1(t), S_2(t), \ldots, S_N(t)$ represent the concentrations of the N corresponding substances at time t. Then the temporal evolution of the system can be described approximately by

$$\frac{dS_j}{dt} = f_j\left(S_1, S_2, \ldots, S_N\right)$$

where the functions f_j express the dependence of S_j on the concentrations of other substances present in the cell. The functions f_j are ultimately derived from basic principles of chemical kinetics or simple expressions derived from these e.g. Michaelis-Menten enzymatic kinetics. Hence, the functional forms of the f_j are usually chosen as low-order polynomials or Hill functions that serve as an ansatz for the real molecular dynamics. Such models are then studied using the mathematics of nonlinear dynamics. System-specific information, like reaction rate constants and sensitivities, are encoded as constant parameters.

By solving for the fixed point of the system:

$$\frac{dS_j}{dt} = 0$$

for all j, one obtains (possibly several) concentration profiles of proteins and mRNAs that are theoretically sustainable (though not necessarily stable). Steady states of kinetic equations thus correspond to potential cell types, and oscillatory solutions to the above equation to naturally cyclic cell types. Mathematical stability of these attractors can usually be characterized by the sign of higher derivatives at critical points, and then correspond to biochemical stability of the concentration profile. Critical points and bifurcations in the equations correspond to critical cell states in which small state or parameter perturbations

could switch the system between one of several stable differentiation fates. Trajectories correspond to the unfolding of biological pathways and transients of the equations to short-term biological events. For a more mathematical discussion, see the articles on nonlinearity, dynamical systems, bifurcation theory, and chaos theory.

Boolean network

The following example illustrates how a Boolean network can model a GRN together with its gene products (the outputs) and the substances from the environment that affect it (the inputs). Stuart Kauffman was amongst the first biologists to use the metaphor of Boolean networks to model genetic regulatory networks.[3]

1. Each gene, each input, and each output is represented by a node in a directed graph in which there is an arrow from one node to another if and only if there is a causal link between the two nodes.
2. Each node in the graph can be in one of two states: on or off.
3. For a gene, "on" corresponds to the gene being expressed; for inputs and outputs, "on" corresponds to the substance being present.
4. Time is viewed as proceeding in discrete steps. At each step, the new state of a node is a Boolean function of the prior states of the nodes with arrows pointing towards it.

The validity of the model can be tested by comparing simulation results with time series observations.

Continuous networks

Continuous network models of GRNs are an extension of the boolean networks described above. Nodes still represent genes and connections between them regulatory influences on gene expression. Genes in biological systems display a continuous range of activity levels and it has been argued that using a continuous representation captures several properties of gene regulatory networks not present in the Boolean model.[4] Formally most of these approaches are similar to an artificial neural network, as inputs to a node are summed up and the result serves as input to a sigmoid function, e.g.,[5] but proteins do often control gene expression in a synergistic, i.e. non-linear, way.[6] However there is now a continuous network model[7] that allows grouping of inputs to a node thus realizing another level of regulation. This model is formally closer to a higher order recurrent neural network. The same model has also been used to mimic the evolution of cellular differentiation[8] and even multicellular morphogenesis.[9]

Stochastic gene networks

Recent experimental results[10] [11] have demonstrated that gene expression is a stochastic process. Thus, many authors are now using the stochastic formalism, after the first work by.[12] Works on single gene expression[13] and small synthetic genetic networks,[14] [15] such as the genetic toggle switch of Tim Gardner and Jim Collins, provided additional experimental data on the phenotypic variability and the stochastic nature of gene expression. The first versions of stochastic models of gene expression involved only instantaneous reactions and were driven by the Gillespie algorithm.[16]

Since some processes, such as gene transcription, involve many reactions and could not be correctly modeled as an instantaneous reaction in a single step, it was proposed to model these reactions as single step multiple delayed reactions in order to account for the time it

takes for the entire process to be complete.[17]

From here, a set of reactions were proposed[18] that allow generating GRNs. These are then simulated using a modified version of the Gillespie algorithm, that can simulate multiple time delayed reactions (chemical reactions where each of the products is provided a time delay that determines when will it be released in the system as a "finished product").

For example, basic transcription of a gene can be represented by the following single-step reaction (RNAP is the RNA polymerase, RBS is the RNA ribosome binding site, and Pro_i is the promoter region of gene *i*):

$$\text{RNAP} + \text{Pro}_i \xrightarrow{k_{i,bas}} \text{Pro}_i(\tau_i^1) + \text{RBS}_i(\tau_i^1) + \text{RNAP}(\tau_i^2)$$
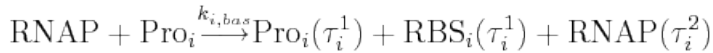
A recent work proposed a simulator (SGNSim, *Stochastic Gene Networks Simulator*),[19] that can model GRNs where transcription and translation are modeled as multiple time delayed events and its dynamics is driven by a stochastic simulation algorithm (SSA) able to deal with multiple time delayed events. The time delays can be drawn from several distributions and the reaction rates from complex functions or from physical parameters. SGNSim can generate ensembles of GRNs within a set of user-defined parameters, such as topology. It can also be used to model specific GRNs and systems of chemical reactions. Genetic perturbations such as gene deletions, gene over-expression, insertions, frame shift mutations can also be modeled as well.

The GRN is created from a graph with the desired topology, imposing in-degree and out-degree distributions. Gene promoter activities are affected by other genes expression products that act as inputs, in the form of monomers or combined into multimers and set as direct or indirect. Next, each direct input is assigned to an operator site and different transcription factors can be allowed, or not, to compete for the same operator site, while indirect inputs are given a target. Finally, a function is assigned to each gene, defining the gene's response to a combination of transcription factors (promoter state). The transfer functions (that is, how genes respond to a combination of inputs) can be assigned to each combination of promoter states as desired.

In other recent work, multiscale models of gene regulatory networks have been developed that focus on synthetic biology applications. Simulations have been used that model all biomolecular interactions in transcription, translation, regulation, and induction of gene regulatory networks, guiding the design of synthetic systems.[20]

Network connectivity

Empirical data indicate that biological gene networks are sparsely connected, and that the average number of upstream-regulators per gene is less than two.[21] Theoretical results show that selection for robust gene networks will favor minimally complex, more sparsely connected, networks.[21] These results suggest that a sparse, minimally connected, genetic architecture may be a fundamental design constraint shaping the evolution of gene network complexity.

See also

- Operon
- Systems biology
- Synexpression
- Cis-regulatory module
- Body plan
- Morphogen

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External links

- Gene Regulatory Networks (http://www.doegenomestolife.org/science/generegulatorynetwork.shtml) — Short introduction
- BIB: Yeast Biological Interaction Browser (http://sergi5.com/bio)
- Graphical Gaussian models for genome data (http://strimmerlab.org/notes/ggm.html) — Inference of gene association networks with GGMs
- A bibliography on learning causal networks of gene interactions (http://www.molgen.mpg.de/~markowet/docs/network-bib.pdf) - regularly updated, contains hundreds of links to papers from bioinformatics, statistics, machine learning.
- http://mips.gsf.de/proj/biorel/BIOREL is a web-based resource for quantitative estimation of the gene network bias in relation to available database information about gene activity/function/properties/associations/interactio.
- Evolving Biological Clocks using Genetic Regulatory Networks (http://panmental.de/GRNclocks) - Information page with model source code and Java applet.
- Engineered Gene Networks (http://www.bu.edu/abl)
- Tutorial: Genetic Algorithms and their Application to the Artificial Evolution of Genetic Regulatory Networks (http://panmental.de/ICSBtut/)

Computational genomics

Computational genomics is the study of deciphering biology from genome sequences using computational analysis.[1] , including both DNA and RNA. Computational genomics focuses on understanding the human genome, and more generally the principles of how DNA controls the biology of any species at the molecular level. With the current abundance of massive biological datasets, computational studies have become one of the most important means to biological discovery. [2]

History

Computational genomics began in spirit, if not in name, during the 1960s with the research of Margaret Dayhoff and others at the National Biomedical Research Foundation, who first assembled a database of protein sequences.[3] Their research developed a phylogenetic tree that determined the evolutionary changes that were required for a particular protein to change into another protein based on the underlying amino acid sequences. This led them to create a scoring matrix that assessed the likelihood of one protein being related to another.

Beginning in the 1980s, databases of genome sequences began to be recorded, but this presented new challenges in the form of searching and comparing the databases of gene information. Unlike text-searching algorithms that are used on websites such as google or Wikipedia, searching for sections of genetic similarity requires one to find strings that are not simply identical, but similar. This led to the development of the Needleman-Wunsch algorithm, which is a dynamic programming algorithm for comparing sets of amino acid sequences with each other by using scoring matrices derived from the earlier research by Dayhoff. Later, the BLAST algorithm was developed for performing fast, optimized searches of gene sequence databases. BLAST and its derivatives are probably the most widely-used algorithms for this purpose. [4]

The first meeting of the Annual Conference on Computational Genomics was in 1998, providing a forum for this speciality and effectively distinguishing this area of science from the more general fields of Genomics or Computational Biology. [5] The first use of this term in scientific literature, according to MEDLINE abstracts, was just one year earlier in Nucleic Acids Research. [6] .

The development of computer-assisted mathematics (using products such as Mathematica or Matlab) has helped engineers, mathematicians and computer scientists to start operating in this domain, and a public collection of case studies and demonstrations is growing, ranging from whole genome comparisons to gene expression analysis. [7] . This has increased the introduction of different ideas, including concepts from systems and control, information theory, strings analysis and data mining. It is anticipated that computational approaches will become and remain a standard topic for research and teaching, while students fluent in both topics start being formed in the multiple courses created in the past few years.

Contributions of computational genomics research to biology

Contributions of computational genomics research to biology include [2] :

- discovering subtle patterns in genomic sequences
- proposing cellular signalling networks
- proposing mechanisms of genome evolution
- predict precise locations of all human genes using [comparative genomics] techniques with several mammalian and vertebrate species
- predict conserved genomic regions that are related to early embryonic development
- discover potential links between repeated sequence motifs and tissue-specific gene expression
- measure regions of genomes that have undergone unusually rapid evolution

See also

- Bioinformatics
- Biowiki
- Computational biology
- Genomics
- Microarray
- BLAST
- Computational epigenetics

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External links

- Harvard Extension School Biophysics 101, Genomics and Computational Biology, http:// www.courses.fas.harvard.edu/~bphys101/info/syllabus.html
- University of Bristol course in Computational Genomics, http://www. computational-genomics.net/

DNA nanotechnology

Part of a series of articles on
Molecular self-assembly
Self-assembled monolayer Supramolecular assembly DNA nanotechnology
See also Nanotechnology

DNA nanotechnology is a subfield of nanotechnology which seeks to use the unique molecular recognition properties of DNA and other nucleic acids to create novel, controllable structures out of DNA. The DNA is thus used as a structural material rather than as a carrier of genetic information, making it an example of bionanotechnology. This has possible applications in molecular self-assembly and in DNA computing.

Introduction: DNA crossover molecules
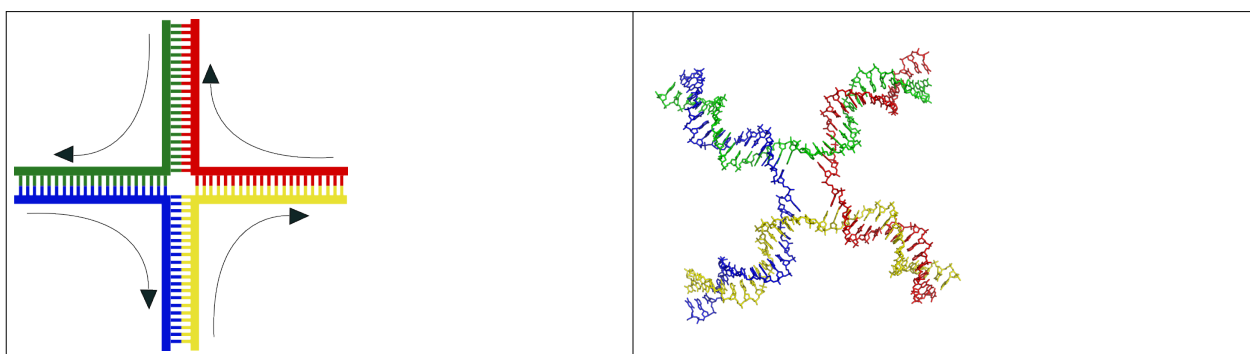
Structure of the 4-arm junction.
Left: A schematic. **Right**: A more realistic model.[1]
Each of the four separate DNA single strands are shown in different colors.

DNA nanotechnology makes use of branched DNA structures to create DNA complexes with useful properties. DNA is normally a linear molecule, in that its axis is unbranched. However, DNA molecules containing junctions can also be made. For example, a four-arm junction can be made using four individual DNA strands which are complementary to each other in the correct pattern. Due to Watson-Crick base pairing, only portions of the strands which are complementary to each other will attach to each other to form duplex DNA. This four-arm junction is an immobile form of a Holliday junction.

Junctions can be used in more complex molecules. The most important of these is the "double-crossover" or DX motif. Here, two DNA duplexes lie next to each other, and share two junction points where strands cross from one duplex into the other. This molecule has the advantage that the junction points are now constrained to a single orientation as opposed to being flexible as in the four-arm junction. This makes the DX motif suitible as a structural building block for larger DNA complexes.[3]
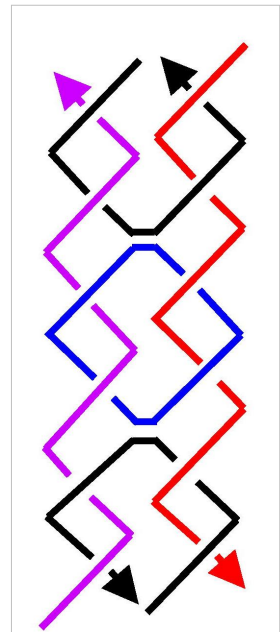
A double-crossover (DX) molecule. This molecule consists of five DNA single strands which form two double-helical domains, on the left and the right in this image. There are two crossover points where the strands cross from one domain into the other. Image from Mao, 2004. [2]

Tile-based arrays

Assembly of a DX array. Each bar represents a double-helical domain of DNA, with the shapes representing comlimentary sticky ends. The DX molecule at top will combine into the two-dimensional DNA array shown at bottom. Image from Mao, 2004. [2]
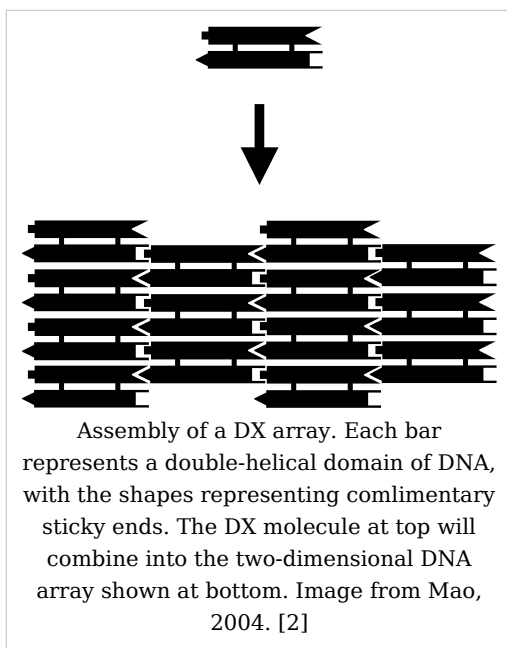
DX arrays

DX, Double Crossover, molecules can be equipped with sticky ends in order to combine them into a two-dimenstional periodic lattice. Each DX molecule has four termini, one at each end of the two double-helical domains, and these can be equipped with sticky ends that program them to combine into a specific pattern. More than one type of DX can be used which can be made to arrange in rows or any other tessellated pattern. They thus form extended flat sheets which are essentially two-dimensional crystals of DNA.[4]

DNA nanotubes

In addition to flat sheets, DX arrays have been made to form hollow tubes of 4-20 nm diameter. These DNA nanotubes are somewhat similar in size and shape to carbon nanotubes, but the carbon nanotubes are stronger and better conductors, whereas the DNA nanotubes are more easily modified and connected to other structures.[5]

Other tile arrays

Two-dimensional arrays have been made out of other motifs as well, including the Holliday junction rhombus array as well as various DX-based arrays in the shapes of triangles and hexagons.[6] Another motif, the six-helix bundle, has the ability to form three-dimensional DNA arrays as well.[7]

DNA origami

As an alternative to the tile-based approach, two-dimensional DNA structures can be made from a single, long DNA strand of arbitrary sequence which is folded into the desired shape by using shorter, "staple" strands. This allows the creation of two-dimensional shapes at the nanoscale using DNA. Demonstrated designs have included the smiley face and a coarse map of North America. DNA origami was the cover story of *Nature* on March 15, 2006.[8]

DNA polyhedra

A number of three-dimensional DNA molecules have been made which have the connectivity of a polyhedron such as an octahedron or cube. In other words, the DNA duplexes trace the edges of a polyhedron with a DNA junction at each vertex. The earliest demonstrations of DNA polyhedra involved multiple ligations and solid-phase synthesis steps to create catenated polyhedra. More recently, there have been demonstrations of a DNA truncated octahedron made from a long single strand designed to fold into the correct conformation, as well as a tetrahedron which can be produced from four DNA strands in a single step.[9]

DNA nanomechanical devices

DNA complexes have been made which change their conformation upon some stimulus. These are intended to have applications in nanorobotics. One of the first such devices, called "molecular tweezers," changes from an open to a closed state based upon the presence of control strands.

DNA machines have also been made which show a twisting motion. One of these makes use of the transition between the B-DNA and Z-DNA forms to respond to a change in buffer conditions. Another relies on the presence of control strands to switch from a paranemic-crossover (PX) conformation to a double-junction (JX2) conformation.[10]

Stem Loop Controllers

A design called a *stem loop*, consisting of a single strand of DNA which has a loop at an end, are a dynamic structure that opens and closes when a piece of DNA bonds to the loop part. This effect has been exploited to create several logic gates. [11] [12] These logic gates have been used to create the computers MAYA I and MAYA II which can play tick-tac-toe to some extent.[13]

Applications

Algorithmic self-assembly

DNA nanotechnology has been applied to the related field of DNA computing. A DX array has been demonstrated whose assembly encodes an XOR operation, which allows the DNA array to implement a cellular automaton which generates a fractal called the Sierpinski gasket. This shows that computation can be incorporated into the assembly of DNA arrays, increasing its scope beyond simple periodic arrays.

Note that DNA computing overlaps with, but is distinct from, DNA nanotechnology. The latter uses the specificity of Watson-Crick basepairing to make novel structures out of DNA. These structures can be used for DNA
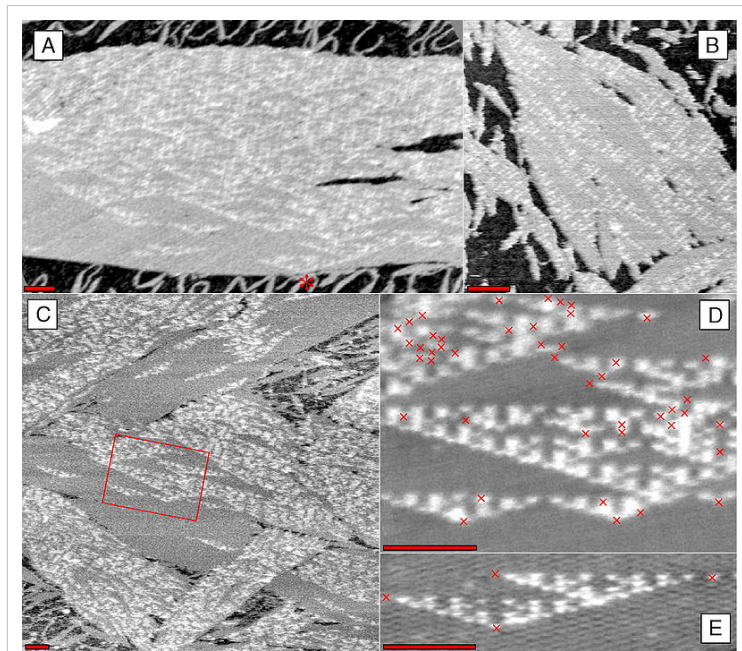
DNA arrays that display a representation of the Sierpinski gasket on their surfaces. Click the image for further details. Image from Rothemund *et al.*, 2004. [14]

computing, but they do not have to be. Additionally, DNA computing can be done without using the types of molecules made possible by DNA Nanotechnology.[15]

Nanoarchitecture

The idea of using DNA arrays to template the assembly of other functional molecules has been around for a while, but only recently has progress been made in reducing these kinds of schemes to practice. In 2006, researchers covalently attached gold nanoparticles to a DX-based tile and showed that self-assembly of the DNA structures also assembled the nanoparticles hosted on them. A non-covalent hosting scheme was shown in 2007, using Dervan polyamides on a DX array to arrange streptavidin proteins on specific kinds of tiles on the DNA array.[16] Previously in 2006 LaBean demonstrated the letters "D" "N" and "A" created on a 4x4 DX array using streptavidin. [17]

DNA has also been used to assemble a single walled carbon nanotube Field-effect transistor.[18]

See also

- Mechanical properties of DNA

External links

- Chengde Mao page at Purdue University [19]
- John Reif lab at Duke University [20]
- Nadrian Seeman lab at NYU [21]
- William M. Shih lab at Harvard Medical School [22]
- Andrew Turberfield lab at Oxford University [23]
- Erik Winfree lab at Caltech [24]
- Hao Yan lab at Arizona State University [25]
- Bernard Yurke formerly at Bell Labs [26] now at Boise State University [27]
- Thom LaBean at Duke University [28]
- Software for 3D DNA design, modeling and/or simulation:
  - Ascalaph Designer [29]
  - caDNAno [30]
  - GIDEON [31]
  - NanoEngineer-1 [32]
- International Society for Nanoscale Science, Computation and Engineering [33]

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Note: Click on the doi to access the text of the referenced article.

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DNA computing

DNA computing is a form of computing which uses DNA, biochemistry and molecular biology, instead of the traditional silicon-based computer technologies. DNA computing, or, more generally, molecular computing, is a fast developing interdisciplinary area. Research and development in this area concerns theory, experiments and applications of DNA computing.

History

This field was initially developed by Leonard Adleman of the University of Southern California, in 1994.[1] Adleman demonstrated a proof-of-concept use of DNA as a form of computation which solved the seven-point Hamiltonian path problem. Since the initial Adleman experiments, advances have been made and various Turing machines have been proven to be constructible.[2] [3]

In 2002, researchers from the Weizmann Institute of Science in Rehovot, Israel, unveiled a programmable molecular computing machine composed of enzymes and DNA molecules instead of silicon microchips. [4] On April 28 2004, Ehud Shapiro, Yaakov Benenson, Binyamin Gil, Uri Ben-Dor, and Rivka Adar at the Weizmann Institute announced in the journal Nature that they had constructed a DNA computer.[5] This was coupled with an input and output module and is capable of diagnosing cancerous activity within a cell, and then releasing an anti-cancer drug upon diagnosis.

Capabilities

DNA computing is fundamentally similar to parallel computing in that it takes advantage of the many different molecules of DNA to try many different possibilities at once.

For certain specialized problems, DNA computers are faster and smaller than any other computer built so far. But DNA computing does not provide any new capabilities from the standpoint of computability theory, the study of which problems are computationally solvable using different models of computation. For example, if the space required for the solution of a problem grows exponentially with the size of the problem (EXPSPACE problems) on von Neumann machines it still grows exponentially with the size of the problem on DNA machines. For very large EXPSPACE problems, the amount of DNA required is too large to be practical. (Quantum computing, on the other hand, *does* provide some interesting new capabilities).

DNA computing overlaps with, but is distinct from, DNA nanotechnology. The latter uses the specificity of Watson-Crick basepairing and other DNA properties to make novel structures out of DNA. These structures can be used for DNA computing, but they do not have to be. Additionally, DNA computing can be done without using the types of molecules made possible by DNA nanotechnology (as the above examples show).

Examples

- MAYA II
- Computational Genes

See also

- Peptide computing
- Parallel computing
- Quantum computing

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- International Meeting on DNA Computing (http://hagi.is.s.u-tokyo.ac.jp/dna/)

Synexpression

Synexpression is a type of non-random eukaryotic gene organization. Genes in a synexpression group may not be physically linked, but they are involved in the same process and they are coordinately expressed. It is expected that genes that function in the same process be regulated coordinately. Synexpression groups in particular represent genes that are simultaneously up- or down-regulated, often because their gene products are required in stoichiometric amounts or are protein-complex subunits. [1] It is likely that these gene groups share common *cis*- and *trans*-acting control elements to achieve coordinate expression.

Synexpression groups are determined mainly by analysis of expression profiles compiled by the use of DNA microarrays. [1] The use of this technology helps researchers monitor changes in expression patterns for large numbers of genes in a given experiment. Analysis of DNA microarray expression profiles has led to the discovery of a number of genes that are tightly co-regulated.[1]

One simplified example of a synexpression group is the genes *cdc6, cdc3, cdc46,* and *swi4* in yeast, which are all co-expressed early in the G-1 stage of the cell cycle.[1] ,[2] These genes share one common *cis*-regulatory element, called ECB, which serves as a binding site for the MCM1 *trans*-acting protein. Although these genes are not spatially clustered, co-regulation seems to be achieved via this common *cis* and *trans* control mechanism. Most synexpression groups are more complicated than the ECB group in yeast, involving a myriad of *cis* and *trans* control elements. [1] , [2]

The identification of synexpression groups has had an impact on the way some scientists view evolutionary change in higher eukaryotes. [1] Since groups of genes involved in the same biological process often share one or more common control elements, it has been suggested that the differential expression of these synexpression groups in different tissues of organisms can contribute to co-evolution tissues, organs, and appendages. [1] Today it is commonly believed that it is not primarily the gene products themselves that evolve, but that it is the control networks for groups of genes that contribute most to the evolution of higher eukaryotes.[1]

Developmental processes provide an example of how changes in synexpression control networks could have a significant impact on an organism's capacity to evolve and adapt effectively. In animals, it is often beneficial for appendages to co-evolve, and it has been observed that fore-and hind-limbs share expression of Hox genes early in metazoan development.[1] Thus, changes in the regulatory patterns of these genes would effect the development of both the fore- and hind-limbs, facilitating co-evolution.

See also

- Gene regulatory network

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Computational epigenetics

Computational epigenetics[1] uses bioinformatic methods to complement experimental research in epigenetics. Due to the recent explosion of epigenome datasets, computational methods play an increasing role in all areas of epigenetic research.

Definition

Research in computational epigenetics comprises the development and application of bioinformatic methods for solving epigenetic questions, as well as computational data analysis and theoretical modeling in the context of epigenetics.

Current research areas

Epigenetic data processing and analysis

Various experimental techniques have been developed for genome-wide mapping of epigenetic information, the most widely used being ChIP-on-chip, ChIP-seq and bisulfite sequencing. All of these methods generate large amounts of data and require efficient ways of data processing and quality control by bioinformatic methods.

Epigenome prediction

A substantial amount of bioinformatic research has been devoted to the prediction of epigenetic information from characteristics of the genome sequence. Such predictions serve a dual purpose. First, accurate epigenome predictions can substitute for experimental data, to some degree, which is particularly relevant for newly discovered epigenetic mechanisms and for species other than human and mouse. Second, prediction algorithms build statistical models of epigenetic information from training data and can therefore act as a first step toward quantitative modeling of an epigenetic mechanism.

Applications in cancer epigenetics

The important role of epigenetic defects for cancer opens up new opportunities for improved diagnosis and therapy. These active areas of research give rise to two questions that are particularly amenable to bioinformatic analysis. First, given a list of genomic regions exhibiting epigenetic differences between tumor cells and controls (or between different disease subtypes), can we detect common patterns or find evidence of a functional relationship of these regions to cancer? Second, can we use bioinformatic methods in order to improve diagnosis and therapy by detecting and classifying important disease subtypes?

Emerging topics

The first wave of research in the field of computational epigenetics was driven by rapid progress of experimental methods for data generation, which required adequate computational methods for data processing and quality control, prompted epigenome prediction studies as a means of understanding the genomic distribution of epigenetic information, and provided the foundation for initial projects on cancer epigenetics. While these topics will continue to be major areas of research and the mere quantity of epigenetic data arising from epigenome projects poses a significant bioinformatic challenge, several additional topics are currently emerging.

- Epigenetic regulatory circuitry: Reverse engineering the regulatory networks that read, write and execute epigenetic codes.
- Population epigenetics: Distilling regulatory mechanisms from the integration of epigenome data with gene expression profiles and haplotype maps for a large sample from a heterogeneous population.
- Evolutionary epigenetics: Learning about epigenome regulation in human (and its medical consequences) by cross-species comparisons.
- Theoretical modeling: Testing our mechanistic and quantitative understanding of epigenetic mechanisms by in silico simulation.
- Statistical genome browsers: Developing a new blend of web services that enable biologists to perform sophisticated genome and epigenome analysis within an easy-to-use genome browser environment.
- Medical epigenetics: Searching for epigenetic mechanisms that play a role in diseases other than cancer, as there is strong circumstantial evidence for epigenetic regulation being involved in mental disorders, autoimmune diseases and other complex diseases.

Sources and further reading

The original version of this article was based on a review paper on computational epigenetics that appeared in the January 2008 issue of the Bioinformatics journal: *Bock, C. and Lengauer, T. (2008) Computational epigenetics. Bioinformatics, 24, 1-10* [2]. This review paper provides >100 references to scientific papers and extensive background information. It is published as open access and can be downloaded freely from the publisher's web page: http://dx.doi.org/10.1093/bioinformatics/btm546 [2].

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Protein-protein interaction

Protein-protein interactions involve not only the direct-contact association of protein molecules but also longer range interactions through the electrolyte, aqueous solution medium surrounding neighbor hydrated proteins over distances from less than one nanometer to distances of several tens of nanometers. Furthermore, such protein-protein interactions are thermodynamically linked functions[1] of dynamically bound ions and water that exchange rapidly with the surrounding solution by comparison with the molecular tumbling rate (or correlation times) of the interacting proteins. Protein associations are also studied from the perspectives of biochemistry, quantum chemistry, molecular dynamics, signal transduction and other metabolic or genetic/epigenetic networks. Indeed, protein-protein interactions are at the core of the entire Interactomics system of any living cell.

The interactions between proteins are important for very numerous—if not all—biological functions. For example, signals from the exterior of a cell are mediated to the inside of that cell by protein-protein interactions of the signaling molecules. This process, called signal transduction, plays a fundamental role in many biological processes and in many diseases (e.g. cancers). Proteins might interact for a long time to form part of a protein complex, a protein may be carrying another protein (for example, from cytoplasm to nucleus or vice versa in the case of the nuclear pore importins), or a protein may interact briefly with another protein just to modify it (for example, a protein kinase will add a phosphate to a target protein). This modification of proteins can itself change protein-protein interactions. For example, some proteins with SH2 domains only bind to other proteins when they are phosphorylated on the amino acid tyrosine while bromodomains specifically recognise acetylated lysines. In conclusion, protein-protein interactions are of central importance for virtually every process in a living cell. Information about these interactions improves our understanding of diseases and can provide the basis for new therapeutic approaches.

Methods to investigate protein-protein interactions

Biochemical methods

As protein-protein interactions are so important there are a multitude of methods to detect them. Each of the approaches has its own strengths and weaknesses, especially with regard to the sensitivity and specificity of the method. A high sensitivity means that many of the interactions that occur in reality are detected by the screen. A high specificity indicates that most of the interactions detected by the screen are also occurring in reality.

- Co-immunoprecipitation is considered to be the gold standard assay for protein-protein interactions, especially when it is performed with endogenous (not overexpressed and not tagged) proteins. The protein of interest is isolated with a specific antibody. Interaction partners which stick to this protein are subsequently identified by western

blotting. Interactions detected by this approach are considered to be real. However, this method can only verify interactions between suspected interaction partners. Thus, it is not a screening approach. A note of caution also is that immunoprecipitation experiments reveal direct and indirect interactions. Thus, positive results may indicate that two proteins interact directly or may interact via a bridging protein.

- Bimolecular Fluorescence Complementation (BiFC) is a new technique in observing the interactions of proteins. Combining with other new techniques, this method can be used to screen protein-protein interactions and their modulators [2].

- Affinity electrophoresis as used for estimation of binding constants, as for instance in lectin affinity electrophoresis or characterization of molecules with specific features like glycan content or ligand binding.

- Pull-down assays are a common variation of immunoprecipitation and immunoelectrophoresis and are used identically, although this approach is more amenable to an initial screen for interacting proteins.

- Label transfer can be used for screening or confirmation of protein interactions and can provide information about the interface where the interaction takes place. Label transfer can also detect weak or transient interactions that are difficult to capture using other *in vitro* detection strategies. In a label transfer reaction, a known protein is tagged with a detectable label. The label is then passed to an interacting protein, which can then be identified by the presence of the label.

- The yeast two-hybrid screen investigates the interaction between artificial fusion proteins inside the nucleus of yeast. This approach can identify binding partners of a protein in an unbiased manner. However, the method has a notorious high false-positive rate which makes it necessary to verify the identified interactions by co-immunoprecipitation.

- *In-vivo* crosslinking of protein complexes using photo-reactive amino acid analogs was introduced in 2005 by researchers from the Max Planck Institute [3] In this method, cells are grown with photoreactive diazirine analogs to leucine and methionine, which are incorporated into proteins. Upon exposure to ultraviolet light, the diazirines are activated and bind to interacting proteins that are within a few angstroms of the photo-reactive amino acid analog.

- Tandem affinity purification (TAP) method allows high throughput identification of protein interactions. In contrast to Y2H approach accuracy of the method can be compared to those of small-scale experiments (Collins et al., 2007) and the interactions are detected within the correct cellular environment as by co-immunoprecipitation. However, the TAP tag method requires two successive steps of protein purification and consequently it can not readily detect transient protein-protein interactions. Recent genome-wide TAP experiments were performed by Krogan et al., 2006 and Gavin et al., 2006 providing updated protein interaction data for yeast organism.

- Chemical crosslinking is often used to "fix" protein interactions in place before trying to isolate/identify interacting proteins. Common crosslinkers for this application include the non-cleavable NHS-ester crosslinker, *bis*-sulfosuccinimidyl suberate (BS3); a cleavable version of BS3, dithiobis(sulfosuccinimidyl propionate) (DTSSP); and the imidoester crosslinker dimethyl dithiobispropionimidate (DTBP) that is popular for fixing interactions in ChIP assays.

- Chemical crosslinking followed by high mass MALDI mass spectrometry can be used to analyze intact protein interactions in place before trying to isolate/identify interacting

proteins. This method detects interactions among non-tagged proteins and is available from CovalX.

- SPINE (Strep-protein interaction experiment) [4] uses a combination of reversible crosslinking with formaldehyde and an incorporation of an affinity tag to detect interaction partners *in vivo*.

- Quantitative immunoprecipitation combined with knock-down (QUICK) relies on co-immunoprecipitation, quantitative mass spectrometry (SILAC) and RNA interference (RNAi). This method detects interactions among endogenous non-tagged proteins[5] . Thus, it has the same high confidence as co-immunoprecipitation. However, this method also depends on the availability of suitable antibodies.

Physical/Biophysical and Theoretical methods

- Dual Polarisation Interferometry (DPI) can be used to measure protein-protein interactions. DPI provides real-time, high-resolution measurements of molecular size, density and mass. While tagging is not necessary, one of the protein species must be immobilized on the surface of a waveguide. As well as kinetics and affinity, conformational changes during interaction can also be quantified.

- Static Light scattering (SLS) measures changes in the Rayleigh scattering of protein complexes in solution and can non-destructively characterize both weak and strong interactions without tagging or immobilization of the protein. The measurement consists of mixing a series of aliquots of different concentrations or compositions with the anylate, measuring the effect of the changes in light scattering as a result of the interaction, and fitting the correlated light scattering changes with concentration to a model. Weak, non-specific interactions are typically characterized via the second virial coefficient. This type of analysis can determine the equilibrium association constant for associated complexes.[6] . Additional light scattering methods for protein activity determination were previously developed by Timasheff. More recent Dynamic Light scattering (DLS) methods for proteins were reported by H. Chou that are also applicable at high protein concentrations and in protein gels; DLS may thus also be applicable for *in vivo* cytoplasmic observations of various protein-protein interactions.

- Surface plasmon resonance can be used to measure protein-protein interaction.

- With Fluorescence correlation spectroscopy, one protein is labeled with a fluorescent dye and the other is left unlabeled. The two proteins are then mixed and the data outputs the fraction of the labeled protein that is unbound and bound to the other protein, allowing you to get a measure of K_D and binding affinity. You can also take time-course measurements to characterize binding kinetics. FCS also tells you the size of the formed complexes so you can measure the stoichiometry of binding. A more powerful methods is [[fluorescence cross-correlation spectroscopy (FCCS) that employs double labeling techniques and cross-correlation resulting in vastly improved signal-to-noise ratios over FCS. Furthermore, the two-photon and three-photon excitation practically eliminates photobleaching effects and provide ultra-fast recording of FCCS or FCS data.

- Fluorescence resonance energy transfer (FRET) is a common technique when observing the interactions of only two different proteins[7] .

- Protein activity determination by NMR multi-nuclear relaxation measurements, or 2D-FT NMR spectroscopy in solutions, combined with nonlinear regression analysis of NMR relaxation or 2D-FT spectroscopy data sets. Whereas the concept of water activity is widely known and utilized in the applied biosciences, its complement--the protein activity

which quantitates protein-protein interactions-- is much less familiar to bioscientists as it is more difficult to determine in dilute solutions of proteins; protein activity is also much harder to determine for concentrated protein solutions when protein aggregation, not merely transient protein association, is often the dominant process[8] .

- Theoretical modeling of protein-protein interactions involves a detailed physical chemistry/thermodynamic understanding of several effects involved, such as intermolecular forces, ion-binding, proton fluctuations and proton exchange. The theory of thermodynamically linked functions is one such example in which ion-binding and protein-protein interactions are treated as linked processes; this treatment is especially important for proteins that have enzymatic activity which depends on cofactor ions dynamically bound at the enzyme active site, as for example, in the case of oxygen-evolving enzyme system (OES) in photosythetic biosystems where the oxygen molecule binding is linked to the chloride anion binding as well as the linked state transition of the manganese ions present at the active site in Photosystem II(PSII). Another example of thermodynamically linked functions of ions and protein activity is that of divalent calcium and magnesium cations to myosin in mechanical energy transduction in muscle. Last-but-not least, chloride ion and oxygen binding to hemoglobin (from several mammalian sources, including human) is a very well-known example of such thermodynamically linked functions for which a detailed and precise theory has been already developed.
- Molecular dynamics (MD) computations of protein-protein interactions.
- Protein-protein docking, the prediction of protein-protein interactions based only on the three-dimensional protein structures from X-ray diffraction of protein crystals might not be satisfactory.[9] [10]

Network visualization of protein-protein interactions

Visualization of protein-protein interaction networks is a popular application of scientific visualization techniques. Although protein interaction diagrams are common in textbooks, diagrams of whole cell protein interaction networks were not as common since the level of complexity made them difficult to generate. One example of a manually produced molecular interaction map is Kurt Kohn's 1999 map of cell cycle control.[11] Drawing on Kohn's map, in 2000 Schwikowski, Uetz, and Fields published a paper on protein-protein interactions in yeast, linking together 1,548 interacting proteins determined by two-hybrid testing. They used a force-directed (Sugiyama) graph drawing algorithm to automatically generate an image of their network.[12] [13] [14] .

An experimental view of Kurt Kohn's 1999 map gmap [15]. Image was merged via gimp 2.2.17 and then uploaded to maplib.net

See also

- Interactomics
- Signal transduction
- Biophysical techniques
- Biochemistry methods
- Genomics
- Complex systems biology
- Complex systems
- Immunoprecipitation
- Protein-protein interaction prediction
- Protein-protein interaction screening
- BioGRID, a public repository for protein and genetic interactions
- Database of Interacting Proteins (DIP)
- NCIBI National Center for Integrative Biomedical Informatics
- Biotechnology
- Protein nuclear magnetic resonance spectroscopy
- 2D-FT NMRI and Spectroscopy
- Fluorescence correlation spectroscopy
- Fluorescence cross-correlation spectroscopy
- Light scattering
- ConsensusPathDB

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External links

- National Center for Integrative Biomedical Informatics (NCIBI) (http://portal.ncibi.org/gateway/)
- Proteins and Enzymes (http://www.dmoz.org/Science/Biology/Biochemistry_and_Molecular_Biology/Biomolecules/Proteins_and_Enzymes/) at the Open Directory Project
- FLIM Applications (http://www.nikoninstruments.com/infocenter.php?n=FLIM) FLIM is also often used in microspectroscopic/ chemical imaging, or microscopic, studies to monitor spatial and temporal protein-protein interactions, properties of membranes and interactions with nucleic acids in living cells.
- Arabidopsis thaliana protein interaction network (http://bioinfo.esalq.usp.br/atpin)

Interactomics

Interactomics is a discipline at the intersection of bioinformatics and biology that deals with studying both the interactions and the consequences of those interactions between and among proteins, and other molecules within a cell[1] . The network of all such interactions is called the Interactome. Interactomics thus aims to compare such networks of interactions (i.e., interactomes) between and within species in order to find how the traits of such networks are either preserved or varied. From a mathematical, or mathematical biology viewpoint an interactome network is a graph or a category representing the most important interactions pertinent to the normal physiological functions of a cell or organism.

Interactomics is an example of "top-down" systems biology, which takes an overhead, as well as overall, view of a biosystem or organism. Large sets of genome-wide and proteomic data are collected, and correlations between different molecules are inferred. From the data new hypotheses are formulated about feedbacks between these molecules. These hypotheses can then be tested by new experiments[2] .

Through the study of the interaction of all of the molecules in a cell the field looks to gain a deeper understanding of genome function and evolution than just examining an individual genome in isolation[1] . Interactomics goes beyond cellular proteomics in that it not only attempts to characterize the interaction between proteins, but between all molecules in the cell.

Methods of interactomics

The study of the interactome requires the collection of large amounts of data by way of high throughput experiments. Through these experiments a large number of data points are collected from a single organism under a small number of perturbations[2] These experiments include:

- Two-hybrid screening
- Tandem Affinity Purification
- X-ray tomography
- Optical fluorescence microscopy

Recent developments

The field of interactomics is currently rapidly expanding and developing. While no biological interactomes have been fully characterized. Over 90% of proteins in *Saccharomyces cerevisiae* have been screened and their interactions characterized, making it the first interactome to be nearly fully specified [3] .

Also there have been recent systematic attempts to explore the human interactome[1] and [4] .

Metabolic Network Model for Escherichia coli.
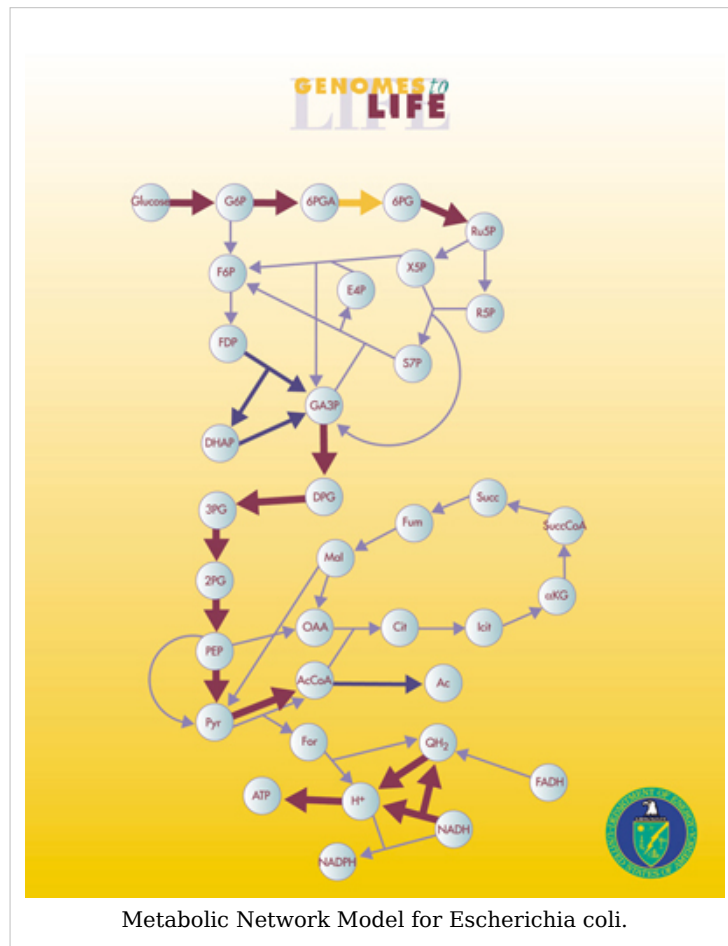
Other species whose interactomes have been studied in some detail include *Caenorhabditis elegans* and *Drosophila melanogaster*.

Criticisms and concerns

Kiemer and Cesareni[1] raise the following concerns with the current state of the field:

- The experimental procedures associated with the field are error prone leading to "noisy results". This leads to 30% of all reported interactions being artifacts. In fact, two groups using the same techniques on the same organism found less than 30% interactions in common.
- Techniques may be biased, i.e. the technique determines which interactions are found.
- Ineractomes are not nearly complete with perhaps the exception of *S. cerivisiae*.
- While genomes are stable, interactomes may vary between tissues and developmental stages.
- Genomics compares amino acids, and nucleotides which are in a sense unchangeable, but interactomics compares proteins and other molecules which are subject to mutation and evolution.
- It is difficult to match evolutionarily related proteins in distantly related species.

See also

- Interaction network
- Proteomics
- Metabolic network
- Metabolic network modelling
- Metabolic pathway
- Genomics
- Mathematical biology
- Systems biology

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External links

- Interactomics.org (http://interactomics.org). A dedicated interactomics web site operated under BioLicense.
- Interactome.org (http://interactome.org). An interactome wiki site.
- PSIbase (http://psibase.kobic.re.kr) Structural Interactome Map of all Proteins.
- Omics.org (http://omics.org). An omics portal site that is openfree (under BioLicense)
- Genomics.org (http://genomics.org). A Genomics wiki site.
- Comparative Interactomics analysis of protein family interaction networks using PSIMAP (protein structural interactome map) (http://bioinformatics.oxfordjournals.org/cgi/content/full/21/15/3234)
- Interaction interfaces in proteins via the Voronoi diagram of atoms (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TYR-4KXVD30-2&_user=10&

_coverDate=11/30/2006&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&
_acct=C000050221&_version=1&_urlVersion=0&_userid=10&
md5=8361bf3fe7834b4642cdda3b979de8bb)

- Using convex hulls to extract interaction interfaces from known structures. Panos Dafas, Dan Bolser, Jacek Gomoluch, Jong Park, and Michael Schroeder. Bioinformatics 2004 20: 1486-1490.
- PSIbase: a database of Protein Structural Interactome map (PSIMAP). Sungsam Gong, Giseok Yoon, Insoo Jang Bioinformatics 2005.
- Mapping Protein Family Interactions : Intramolecular and Intermolecular Protein Family Interaction Repertoires in the PDB and Yeast, Jong Park, Michael Lappe & Sarah A. Teichmann,J.M.B (2001).
- Semantic Systems Biology (http://www.semantic-systems-biology.org)

Developmental biology

Developmental biology is the study of the process by which organisms grow and develop. Modern developmental biology studies the genetic control of cell growth, differentiation and "morphogenesis," which is the process that gives rise to tissues, organs and anatomy. Developmental biology is that branch of life science, which deals with the study of the process by which organisms grow and develop.

"Views of a Fetus in the Womb", Leonardo da Vinci, ca. 1510-1512. The subject of prenatal development is a major subset of developmental biology.

Related fields of study

Embryology is a subfield, the study of organisms between the one-cell stage (generally, the zygote) and the end of the embryonic stage. Embryology was originally a more descriptive science until the 20th century. Embryology and developmental biology today deal with the various steps necessary for the correct and complete formation of the body of a living organism.

The related field of evolutionary developmental biology was formed largely in the 1990s and is a synthesis of findings from molecular developmental biology and evolutionary biology which considers the diversity of organismal form in an evolutionary context.

Perspectives

Animal development is a spectacular process and represents a masterpiece of temporal and spatial control of gene expression. Developmental genetics is a very helpful process. It studies the effect that genes have in a phenotype. The findings of developmental biology can help to understand developmental malfunctions such as chromosomal aberrations, for example, Down syndrome. An understanding of the specialization of cells during embryogenesis may yield information on how to specialize stem cells to specific tissues and organs, which could lead to the specific cloning of organs for medical purposes. Another biologically important process that occurs during development is apoptosis - programmed cell death or "suicide". For this reason, many developmental models are used to elucidate the physiology and molecular basis of this cellular process. Similarly, a deeper understanding of developmental biology can foster greater progress in the treatment of congenital disorders and diseases, e.g. studying human sex determination can lead to treatment for disorders such as congenital adrenal hyperplasia.

Developmental model organisms

Often used model organisms in developmental biology include the following:

- Vertebrates
  - Zebrafish *Danio rerio*[1]
  - Medakafish *Oryzias latipes*
  - Fugu (pufferfish) *Takifugu rubripes*
  - Frog *Xenopus laevis*, *Xenopus tropicalis*[2]
  - Chicken *Gallus gallus*
  - Mouse *Mus musculus* (Mammalian embryogenesis)[3]
- Invertebrates
  - Lancelet *Branchiostoma lanceolatum*
  - Ascidian *Ciona intestinalis*
  - Sea urchin *Strongylocentrotus purpuratus*
  - Roundworm *Caenorhabditis elegans*
  - Fruit fly *Drosophila melanogaster* (Drosophila embryogenesis)
- Plants (Plant embryogenesis)
  - *Arabidopsis thaliana*
  - Maize
  - Snapdragon *Antirrhinum majus*
- Other
  - Slime mold *Dictyostelium discoideum*

Studied phenomena

Cell differentiation

Differentiation is the formation of cell types, from what is originally one cell – the zygote or spore. The formation of cell types like nerve cells occurs with a number of intermediary, less differentiated cell types. A cell stays a certain cell type by maintaining a particular pattern of gene expression.[4] This depends on regulatory genes, e.g. for transcription factors and signaling proteins. These can take part in self-perpetuating circuits in the gene

regulatory network, circuits that can involve several cells that communicate with each other.[5] External signals can alter gene expression by activating a receptor, which triggers a signaling cascade that affects transcription factors. For example, the withdrawal of growth factors from myoblasts causes them to stop dividing and instead differentiate into muscle cells.[6]

Embryonal development

Embryogenesis is the step in the life cycle after fertilisation – the development of the embryo, starting from the zygote (fertilised egg). Organisms can differ drastically in the how embryo develops, especially when belong to different phyla. For example, embryonal development in placental mammals starts with cleavage of the zygote into eight uncommited cells, which then form a ball (morula). The outer cells become the trophectoderm which will form the fetal part of the placenta, while inner cells become the inner cell mass that will form all other organs. In contrast, the fruit fly zygote first forms a sausage-shaped syncytium, which is still one cell but with many cell nuclei.[7]

Patterning is important for determining which cells develop which organs. This is mediated by signaling between adjacent cells by proteins on their surfaces, and by gradients of signaling molecules.[8] An example is retinoic acid, which forms a gradient in the head to tail direction in animals. Retinoic acid enters cells and activates Hox genes in a concentration-dependent manner – Hox genes differ in how much retinoic acid they require for activation. As Hox genes code for transcription factors, this causes discrete segments in the head to tail direction.[9] This is important for e.g. the segmentation of the spine in vertebrates.[8]

Embryonal development does not always go right, and errors can result in birth defects or miscarriage. Often the reason is genetic (mutation or chromosome abnormality), but there can be environmental influence (teratogens).[10] Abnormal development is also of evolutionary interest as it provides a mechanism for changes in body plan (*see evolutionary developmental biology*).[11]

Growth

Growth is the enlargement of a tissue or organism. Growth continues after the embryonal stage, and occurs through cell proliferation, enlargement of cells or accumulation of extracellular material. In plants, growth results in an adult organism that is strikingly different from the embryo. The proliferating cells tend to be distinct from differentiated cells (*see stem cell and progenitor cell*). In some tissues proliferating cells are restricted to specialised areas, such as the growth plates of bones.[12] But some stem cells migrate to where they are needed, such as mesenchymal stem cells which can migate from the bone marrow to form e.g. muscle, bone or adipose tissue.[13] The size of an organ frequently determines its growth, as in the case of the liver which grows back to its previous size if a part is removed. Growth factors, such as fibroblast growth factors in the animal embryo and growth hormone in juvenile mammals, also control the extent of growth.[12]

Metamorphosis

Most animals have a larval stage, with a body plan different from that of the adult organism. The larva abrubtly develops into an adult in a process called metamorphosis. For example, butterfly larvae (caterpillars) are specilised for feeding whereas adult butterflies (imagos) are specilised for flight and reproduction. When the caterpillar has grown enough, it turns into an immobile pupa. Here, the imago develops from imaginal discs found inside the larva.[14]

Regeneration

Regeneration is the reactivation of development so that a missing body part grows back. This phenomenon has been studied particularly in salamanders, where the adults can reconstruct a whole limb after it has been amputated.[15] Researchers hope to one day be able to induce regeneration in humans (*see regenerative medicine*).[16] There is little spontaneous regeneration in adult humans, although the liver is a notable exception. Like for salamanders, the regeneration of the liver involves dedifferentiation of some cells to a more embryonal state.[15]

Developmental systems biology

Computer simulation of multicellular development is a research methodology to understand the function of the very complex processes involved in the development of organisms. This includes simulation of cell signaling, multicell interactions and regulatory genomic networks in development of multicellular structures and processes (see French flag model or *Biological Physics of the Developing Embryo* for literature). *Minimal genomes* for minimal multicellular organisms may pave the way to understand such complex processes *in vivo*.

See also

- Altricial and Precocial
- Auxology
- Body plan
- Cell signaling
- Embryogenesis
- Embryology
- Evolutionary developmental biology
- Plant evolutionary developmental biology
- Fertilization
- Fish development

- Cell signaling networks
- Developmental noise
- Enhancer
- Enhanceosome
- Gene regulatory network
- Promoter
- Signal transduction
- Transcription factor

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External links

- Developmental Biology of Plants and Animals (http://developmentalbiology.de/en/)
- Developmental Biology - 8th Edition (http://8e.devbio.com) by Scott Gilbert (online textbook)

Cellular differentiation

In developmental biology, **cellular differentiation** is the process by which a less specialized cell becomes a more specialized cell type. Differentiation occurs numerous times during the development of a multicellular organism as the organism changes from a single zygote to a complex system of tissues and cell types. Differentiation is a common process in adults as well: adult stem cells divide and create fully-differentiated daughter cells during tissue repair and during normal cell turnover. Differentiation dramatically changes a cell's size, shape, membrane potential, metabolic activity, and responsiveness to signals.

In the center of the diagram the early steps in the development of a mammal. On the top and bottom are some of the fully-differentiated cell types that will eventually form in the adult.
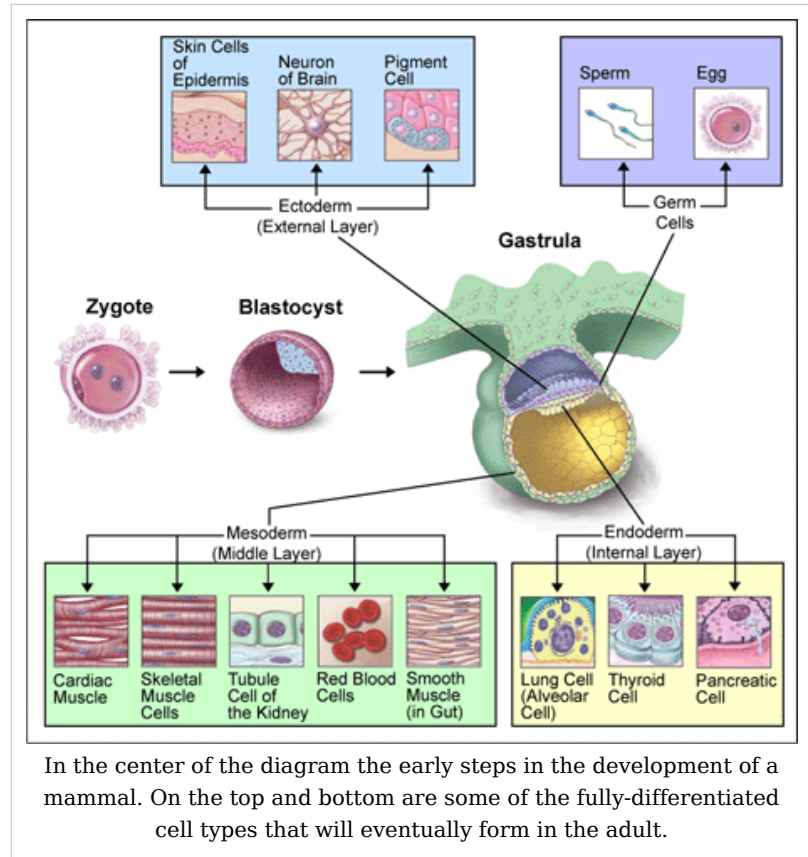
These changes are largely due to highly-controlled modifications in gene expression. With a few exceptions, cellular differentiation almost never involves a change in the DNA sequence itself. Thus, different cells can have very different physical characteristics despite having the same genome.

A cell that is able to differentiate into many cell types is known as *pluripotent*. Such cells are called stem cells in animals and meristematic cells in higher plants. A cell that is able to differentiate into all cell types is known as *totipotent*. In mammals, only the zygote and early embryonic cells are totipotent, while in plants many differentiated cells can become totipotent with simple laboratory techniques. In cytopathology, the level of cellular differentiation is used as a measure of cancer progression. "Grade" is a marker of how differentiated a cell in a tumor is.

Mammalian cell types

Three basic categories of cells make up the mammalian body: germ cells, somatic cells, and stem cells. Each of the approximately 100,000,000,000,000 (10^{14}) cells in an adult human has its own copy or copies of the genome except certain cell types, such as red blood cells, that lack nuclei in their fully differentiated state. Most cells are diploid; they have two copies of each chromosome. Such cells, called somatic cells, make up most of the human body, such as skin and muscle cells. Cells differentiate to specialize for different functions.

Germ line cells are any line of cells that give rise to gametes—eggs and sperm—and thus are continuous through the generations. Stem cells, on the other hand, have the ability to

divide for indefinite periods and to give rise to specialized cells. They are best described in the context of normal human development.

Development begins when a sperm fertilizes an egg and creates a single cell that has the potential to form an entire organism. In the first hours after fertilization, this cell divides into identical cells. In humans, approximately four days after fertilization and after several cycles of cell division, these cells begin to specialize, forming a hollow sphere of cells, called a blastocyst. The blastocyst has an outer layer of cells, and inside this hollow sphere, there is a cluster of cells called the inner cell mass. The cells of the inner cell mass will go on to form virtually all of the tissues of the human body. Although the cells of the inner cell mass can form virtually every type of cell found in the human body, they cannot form an organism. These cells are referred to as pluripotent.

Pluripotent stem cells undergo further specialization into multipotent progenitor cells that then give rise to functional cells. Examples of stem and progenitor cells include:

- *Hematopoietic stem cells* (adult stem cells) from the bone marrow that give rise to red blood cells, white blood cells, and platelets
- *Mesenchymal stem cells* (adult stem cells) from the bone marrow that give rise to stromal cells, fat cells, and types of bone cells
- *Epithelial stem cells* (progenitor cells) that give rise to the various types of skin cells
- *Muscle satellite cells* (progenitor cells) that contribute to differentiated muscle tissue

Dedifferentiation

Dedifferentiation is a cellular process often seen in more basal life forms such as worms and amphibians in which a partially or terminally differentiated cell reverts to an earlier developmental stage, usually as part of a regenerative process.[1] [2] Dedifferentiation also occurs in plants[3] . Cells in cell culture can lose properties they originally had, such as protein expression, or change shape. This process is also termed dedifferentiation[4] .

Some believe dedifferentiation is an aberration of the normal development cycle that results in cancer,[5] whereas others believe it to be a natural part of the immune response lost by humans at some point as a result of evolution.

A small molecule dubbed reversine, a purine analog, has been discovered that has proven to induce dedifferentiation in myotubes. These dedifferentiated cells were then able to redifferentiate into osteoblasts and adipocytes.[6]

Mechanisms

Each specialized cell type in an organism expresses a subset of all the genes that constitute the genome of that species. Each cell type is defined by its particular pattern of regulated gene expression. Cell differentiation is thus a transition of a cell from one cell type to another and it involves a switch from one pattern of gene expression to another. Cellular differentiation during development can be understood as the result of a gene regulatory network. A regulatory gene and its cis-regulatory modules are nodes in a gene regulatory network; they receive input and create output elsewhere in the network [7] . The systems biology approach to developmental biology emphasizes the importance of investigating how developmental mechanisms interact to produce predictable patterns (morphogenesis).

A few evolutionarily conserved types of molecular processes are often involved in the cellular mechanisms that control these switches. The major types of molecular processes

that control cellular differentiation involve cell signaling. Many of the signal molecules that convey information from cell to cell during the control of cellular differentiation are called growth factors. Although the details of specific signal transduction pathways vary, these pathways often share the following general steps. A ligand produced by one cell binds to a receptor in the extracellular region of another cell, inducing a conformational change in the receptor. The shape of the cytoplasmic domain of the receptor changes, and the receptor acquires enzymatic activity. The receptor then catalyzes reactions that phosphorylate other proteins, activating them. A cascade of phosphorylation reactions eventually activates a dormant transcription factor or cytoskeletal protein, thus contributing to the differentiation process in the target cell [8] . Cells and tissues can vary in competence, their ability to respond to external signals [9] .

Induction refers to cascades of signaling events, during which a cell or tissue signals to another cell or tissue to influence its developmental fate [9] . Yamamoto and Jeffery[10] investigated the role of the lens in eye formation in cave- and surface-dwelling fish, a striking example of induction[9] . Through reciprocal transplants, Yamamoto and Jeffery[10] found that the lens vesicle of surface fish can induce other parts of the eye to develop in cave- and surface-dwelling fish, while the lens vesicle of the cave-dwelling fish cannot[9] .

Other important mechanisms fall under the category of asymmetric cell divisions, divisions which give rise to daughter cells with distinct developmental fates. Asymmetric cell divisions can occur because of segregation of cytoplasmic determinants or because of signaling [9] . In the former mechanism, distinct daughter cells are created during cytokinesis because of an uneven distribution of regulatory molecules in the parent cell; the distinct cytoplasm that each daughter cell inherits results in a distinct pattern of differentiation for each daughter cell. A well-studied example of pattern formation by asymmetric divisions is body axis patterning in Drosophila. RNA molecules are an important type of intracellular differentiation control signal. The molecular and genetic basis of asymmetric cell divisions has also been studied in green algae of the genus *Volvox*, a model system for studying how unicellular organisms can evolve into multicellular organisms [9] . In *Volvox carteri*, the 16 cells in the anterior hemisphere of a 32-celled embryo divide asymmetrically, each producing one large and one small daughter cell. The size of the cell at the end of all cell divisions determines whether it will become a specialized germ or somatic cell [9] [11] .

See also

- Morphogenesis
- Multipotent
- Germ layer
- Cell fate determination

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Morphogenesis

Morphogenesis (from the Greek *morphê* shape and *genesis* creation, literally, "beginning of the shape"), is the biological process that causes an organism to develop its shape. It is one of three fundamental aspects of developmental biology along with the control of cell growth and cellular differentiation. The process controls the organized spatial distribution of cells during the embryonic development of an organism. Morphogenetic responses may be induced in organisms by hormones, by environmental chemicals ranging from substances produced by other organisms to toxic chemicals or radionuclides released as pollutants, and other plants, or by mechanical stresses induced by spatial patterning of the cells. Morphogenesis can take place in an embyro, a mature organism, in cell culture or inside tumor cell masses.

Morphogenesis also describes the development of unicellular life forms that do not have an embryonic stage in their life cycle, or describes the evolution of a body structure within a taxonomic group.

History

Some of the earliest ideas on how physical and mathematical processes and constraints affect biological growth were written by D'Arcy Wentworth Thompson and Alan Turing. These works postulated the presence of chemical signals and physico-chemical processes such as diffusion, activation, and deactivation in cellular and organismic growth. The fuller understanding of the mechanisms involved in actual organisms required the discovery of DNA and the development of molecular biology and biochemistry.

Molecular basis

Several types of molecules are particularly important during morphogenesis. Morphogens are soluble molecules that can diffuse and carry signals that control cell differentiation decisions in a concentration-dependent fashion. Morphogens typically act through binding to specific protein receptors. An important class of molecules involved in morphogenesis are transcription factor proteins that determine the fate of cells by interacting with DNA. These can be coded for by master regulatory genes and either activate or deactivate the transcription of other genes; in turn, these secondary gene products can regulate the expression of still other genes in a regulatory cascade. Another class of molecules involved in morphogenesis are molecules that control cell adhesion. For example, during gastrulation, clumps of stem cells switch off their cell-to-cell adhesion, become migratory, and take up new positions within an embryo where they again activate specific cell adhesion proteins and form new tissues and organs. Several examples that illustrate the roles of morphogens, transcription factors and cell adhesion molecules in morphogenesis are discussed below.

Cellular basis

Morphogenesis arises because of changes in the cellular structure or how cells interact in tissues[1] . Certain cell types "sort out". Cell "sorting out" means that when the cells physically interact they move so as to sort into clusters that maximize contact between cells of the same type. The ability of cells to do this comes from differential cell adhesion. Two well-studied types of cells that sort out are epithelial cells and mesenchymal cells. During embryonic development there are some cellular differentiation events during which mesenchymal cells become epithelial cells and at other times epithelial cells differentiate into mesenchymal cells (see Epithelial-mesenchymal transition). Following epithelial-mesenchymal transition, cells can migrate away from an epithelium and then associate with other similar cells in a new location.

Example of cell sorting out with cultured P19 embryonal carcinoma cells. Live cells were stained with either DiI (red) or DiO (green). The red cells were genetically altered and express higher levels of E-cadherin than the green cells. After labeling, the two populations of cells were mixed and cultured together allowing the cells to form large multi-cellular mixed aggregates. Individual cells are less than 10 micrometres in diameter. The image was captured by scanning confocal microscopy.

Adhesion

During embryonic development, cells sort out in different layers due to differential adhesion. Cells that share the same cell-to-cell adhesion molecules separate from cells that have different adhesion molecules. Cells sort based upon differences in adhesion between the cells, so even two populations of cells with different levels of the same adhesion molecule can sort out. In cell culture cells that have the strongest adhesion move to the center of a mixed aggregates of cells.

The molecules responsible for adhesion are called **cell adhesion molecules (CAMs)**. Several types of cell adhesion molecules are known and one major class of these molecules are cadherins. There are dozens of different cadherins that are expressed on different cell types. Cadherins bind to other cadherins in a like-to-like manner: E-cadherin (found on many epithelial cells) binds preferentially to other E-cadherin molecules. Mesenchymal cells usually express other cadherin types such as N-cadherin.

Extracellular Matrix

The extracellular matrix (ECM) is involved with separating tissues, providing structural support or providing a structure for cells to migrate on. Collagen, laminin, and fibronectin are major ECM molecules that are secreted and assembled into sheets, fibers, and gels. Multisubunit transmembrane receptors called integrins are used to bind to the ECM. Integrins bind extracellularly to fibronectin, laminin, or other ECM components, and intracellularly to microfilament-binding proteins α-actinin and talin to link the cytoskeleton with the outside. Integrins also serve as receptors to trigger signal transduction cascades when binding to the ECM. A well-studied example of morphogenesis that involves ECM is mammary gland ductal branching[2],[3].

See also

- Embryogenesis
- Pattern formation
- French flag model
- Reaction-diffusion
- Neurulation
- Gastrulation
- Axon guidance
- Eye development
- Polycystic kidney disease 2
- Drosophila embryogenesis
- Manuel DeLanda

References

[1] Gilbert, Scott F. (2000). http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=morphogenesis&rid=dbio.section.372|"Morphogenesis and Cell Adhesion". *Developmental biology* (6th ed.). Sunderland, Mass: Sinauer Associates. ISBN 0-87893-243-7.

[2] Fata JE, Werb Z, Bissell MJ (2004). "http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=314442|Regulation of mammary gland branching morphogenesis by the extracellular matrix and its remodeling enzymes". *Breast Cancer Res.* **6** (1): 1–11. doi: 10.1186/bcr634 (http://dx.doi.org/10.1186/bcr634). PMID 14680479.

[3] Sternlicht MD (2006). "http://breast-cancer-research.com/content/8/1/201|Key stages in mammary gland development: the cues that regulate ductal branching morphogenesis". *Breast Cancer Res.* **8** (1): 201. doi: 10.1186/bcr1368 (http://dx.doi.org/10.1186/bcr1368). PMID 16524451. PMC: 1413974 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1413974). http://breast-cancer-research.com/content/8/1/201.

External links

- Artificial Life model of multicellular morphogenesis with autonomously generated gradients for positional information (http://panmental.de/ALifeXIflag)

Nuclear medicine

Nuclear medicine is a branch of medicine and medical imaging that uses radioactive isotopes (radionuclides) in the diagnosis and treatment of disease. Nuclear medicine thus relies on the process of radioactive decay. Molecular imaging may employ nuclear medical techniques when it uses radioisotopes to produce images that reflect biological processes that take place at the cellular and sub cellular level.

Nuclear medicine procedures use pharmaceuticals that have been labeled with radionuclides (radiopharmaceuticals). In diagnosis, radioactive substances are administered to patients and the radiation emitted is detected. The diagnostic tests involve the formation of an image using a gamma camera or positron emission tomography, invented by Hal O. Anger, and sometimes called an Anger gamma camera, as well as single photon emission tomography SPECT. Imaging may also be referred to as **radionuclide imaging** or **nuclear scintigraphy**. Other diagnostic tests use probes to acquire measurements from parts of the body, or counters for the measurement of samples taken from the patient.

In therapeutic use, radionuclides may be administered to treat disease, or provide palliative pain relief. To a large extent therapeutic nuclear medicine is an emerging field, although a few isotopes, such as iodine-131 have long been used therapeutically.[1] . Use of radiation from radioisotopes (such as cobalt-60) external to the body has merged with the practice of radiotherapy (**Radiation therapy medicine**), where these radionuclides are used by practioners who also employ other sources of radiation. See radiotherapy for discussion of the therapeutic use of external radioisotopes. Finally, the use of implanted capsules of isotopes (brachytherapy) may be handled by nuclear medicine or radiation therapy medicine.

Nuclear medicinal tests differ from most other imaging modalities in that diagnostic tests primarily show the physiological function of the system being investigated as opposed to traditional anatomical imaging such as CT or MRI. In some centers, the nuclear medicine images can be superimposed, using software or hybrid cameras, on images from modalities such as CT or MRI to highlight the part of the body in which the radiopharmaceutical is concentrated. This practice is often referred to as image fusion or co-registration.

Nuclear medicine diagnostic tests are usually provided by a dedicated department within a hospital and may include facilities for the preparation of radiopharmaceuticals. The specific name of a department can vary from hospital to hospital, with the most common names being the nuclear medicine department and the radioisotope department. Nuclear medicine is a technologically embedded speciality that requires collaboration of not only physicians (nuclear medicine physicians or radiologists), technologists, and support personnel, but also medical physicists, engineers, radiochemists, radiopharmacists, radiobiologists, and instrument manufacturers.

Source of radioisotopes

About two thirds of the world's supply of medical isotopes are produced at the Chalk River Laboratories in Chalk River, Ontario, Canada. The Canadian Nuclear Safety Commission ordered the NRU reactor to be shut down on November 18, 2007 for regularly scheduled maintenance and an upgrade of the safety systems to modern standards. The upgrade took longer than expected and in December 2007 a critical shortage of medical isotopes occurred. The Canadian government unanimously passed emergency legislation, allowing the reactor to re-start on 16 December 2007, and production of medical isotopes to continue.

The Chalk River reactor is used to irradiate materials with neutrons which are produced in great quantity during the fission of U-235. These neutrons change the nucleus of the irradiated material by adding a neutron. For example, the second most commonly used radionuclide is Tc-99m, following the most commonly used radionuclide, F-18 (which is produced by accelerator bombardment of O-18 with protons. The O-18 constitutes about 0.20% of ordinary oxygen (mostly O-16), from which it is extracted; see FDG).

In a reactor, one of the fission products of uranium is Molybdenum-99 which is extracted and shipped to radiopharmaceutical houses all over North America. The Mo-99 radioactively beta decays with a half-life of 2.7 days, turning initially into Tc-99m, which is then extracted (milked) from a "Moly cow" (see technetium-99m generator). The Tc-99m then further decays, while inside a patient, releasing a gamma photon which is detected by the gamma camera. It decays to its ground state of Tc-99, which is relatively non-radioactive compared to Tc-99m.

Diagnostic testing

Diagnostic tests in nuclear medicine exploit the way that the body handles substances differently when there is disease or pathology present. The radionuclide introduced into the body is often chemically bound to a complex that acts characteristically within the body; this is commonly known as a tracer. In the presence of disease, a tracer will often be distributed around the body and/or processed differently. For example, the ligand methylene-diphosphonate (MDP) can be preferentially taken up by bone. By chemically attaching technetium-99m to MDP, radioactivity can be transported and attached to bone via the hydroxyapatite for imaging. Any increased physiological function, such as due to a fracture in the bone, will usually mean increased concentration of the tracer. This often results in the appearance of a 'hot-spot' which is a focal increase in radio-accumulation, or a general increase in radio-accumulation throughout the physiological system. Some disease processes result in the exclusion of a tracer, resulting in the appearance of a 'cold-spot'. Many tracer complexes have been developed in order to image or treat many different organs, glands, and physiological processes. The types of tests can be split into two broad groups: *in-vivo* and *in-vitro*:

Types of diagnostic studies

Common isotopes used in nuclear medicine

isotope	symbol	Z	$T_{1/2}$	decay	photons	β
Imaging:						
fluorine-18	^{18}F	9	110 m	β^+	511 (193%)	0.664 (97%)
gallium-67	^{67}Ga	31	3.26 d	ec	93 (39%), 185 (21%), 300 (17%)	-
krypton-81m	^{81m}Kr	36	13.1 s	IT	190 (68%)	-
rubidium-82	^{82}Rb	37	1.27 m	β^+	511 (191%)	3.379 (95%)
technetium-99m	^{99m}Tc	43	6.01 h	IT	140 (89%)	-
indium-111	^{111}In	49	2.80 d	ec	171 (90%), 245 (94%)	-
iodine-123	^{123}I	53	13.3 h	ec	159 (83%)	-
xenon-133	^{133}Xe	54	5.24 d	β^-	81 (31%)	0.364 (99%)
thallium-201	^{201}Tl	81	3.04 d	ec	69-83* (94%), 167 (10%)	-
Therapy:						
yttrium-90	^{90}Y	39	2.67 d	β^-	-	2.280 (100%)
iodine-131	^{131}I	53	8.02 d	β^-	364 (81%)	0.807 (100%)

Z = atomic number, the number of protons; $T_{1/2}$ = half-life; decay = mode of decay
photons = principle photon energies in kilo-electron volts, keV, (abundance/decay)
β = beta maximum energy in mega-electron volts, MeV, (abundance/decay)
β^+ = β^+ decay; β^- = β^- decay; IT = isomeric transition; ec = electron capture
* X-rays from progeny, mercury, Hg

A typical nuclear medicine study involves administration of a radionuclide into the body by intravenous injection in liquid or aggregate form, ingestion while combined with food, inhalation as a gas or aerosol, or rarely, injection of a radionuclide that has undergone micro-encapsulation. Some studies require the labeling of a patient's own blood cells with a radionuclide (leukocyte scintigraphy and red blood cell scintigraphy). Most diagnostic radionuclides emit gamma rays, while the cell-damaging properties of beta particles are used in therapeutic applications. Refined radionuclides for use in nuclear medicine are derived from fission or fusion processes in nuclear reactors, which produce radioisotopes with longer half-lives, or cyclotrons, which produce radioisotopes with shorter half-lives, or take advantage of natural decay processes in dedicated generators, i.e. molybdenum/technetium or strontium/rubidium.

The most commonly used intravenous radionuclides are:

- Technetium-99m (technetium-99m)
- Iodine-123 and 131
- Thallium-201
- Gallium-67

- Fluorine-18 Fluorodeoxyglucose
- Indium-111 Labeled Leukocytes

The most commonly used gaseous/aerosol radionuclides are:

- Xenon-133
- Krypton-81m
- Technetium-99m Technegas [2]
- Technetium-99m DTPA

Analysis

The end result of the nuclear medicine imaging process is a "dataset" comprising one or more images. In multi-image datasets the array of images may represent a time sequence (ie. cine or movie) often called a "dynamic" dataset, a cardiac gated time sequence, or a spatial sequence where the gamma-camera is moved relative to the patient. SPECT (single photon emission computed tomography) is the process by which images acquired from a rotating gamma-camera are reconstructed to produce an image of a "slice" through the patient at a particular position. A collection of parallel slices form a slice-stack, a three-dimensional representation of the distribution of radionuclide in the patient.

The nuclear medicine computer may require millions of lines of source code to provide quantitative analysis packages for each of the specific imaging techniques available in nuclear medicine.

Time sequences can be further analysed using kinetic models such as multi-compartment models or a Patlak plot.

Radiation dose

A patient undergoing a nuclear medicine procedure will receive a radiation dose. Under present international guidelines it is assumed that any radiation dose, however small, presents a risk. The radiation doses delivered to a patient in a nuclear medicine investigation present a very small risk of inducing cancer. In this respect it is similar to the risk from X-ray investigations except that the dose is delivered internally rather than from an external source such as an X-ray machine.

The radiation dose from a nuclear medicine investigation is expressed as an effective dose with units of sieverts (usually given in millisieverts, mSv). The effective dose resulting from an investigation is influenced by the amount of radioactivity administered in megabecquerels (MBq), the physical properties of the radiopharmaceutical used, its distribution in the body and its rate of clearance from the body.

Effective doses can range from 6 μSv (0.006 mSv) for a 3 MBq chromium-51 EDTA measurement of glomerular filtration rate to 37 mSv for a 150 MBq thallium-201 non-specific tumour imaging procedure. The common bone scan with 600 MBq of technetium-99m-MDP has an effective dose of 3 mSv (1).

Formerly, units of measurement were the curie (Ci), being 3.7E10 Bq, and also 1.0 grams of Radium (Ra-226); the rad (radiation absorbed dose), now replaced by the gray; and the rem (Röntgen equivalent man), now replaced with the sievert. The rad and rem are essentially equivalent for almost all nuclear medicine procedures, and only alpha radiation will produce a higher Rem or Sv value, due to its much higher Relative Biological Effectiveness (RBE). Alpha emitters are nowadays rarely used in nuclear medicine, but were used

extensively before the advent of nuclear reactor and accelerator produced radioisotopes. The concepts involved in radiation exposure to humans is covered by the field of Health Physics.

Notes

[1] http://www.radiomedix.com/RD_AboutTNM.htm
[2] http://jcsmr.anu.edu.au/technegas/home.html

Further reading

- Patient's guide to nuclear medicine
  - Mas JC: A Patient's Guide to Nuclear Medicine Procedures: English-Spanish. Society of Nuclear Medicine, 2008. ISBN 978-0972647892
- Physician's guides to nuclear medicine
  - Taylor A, Schuster DM, Naomi Alazraki N: A Clinicians' Guide to Nuclear Medicine, 2nd edition. Society of Nuclear Medicine, 2000. ISBN 978-0932004727
  - Mark J. Shumate MJ, Kooby DA, Alazraki NP: A Clinician's Guide to Nuclear Oncology: Practical Molecular Imaging and Radionuclide Therapies. Society of Nuclear Medicine, January 2007. ISBN 978-0972647885
- Textbook of nuclear medicine
  - Ell P, Gambhir S: Nuclear Medicine in Clinical Diagnosis and Treatment. Churchill Livingstone, 2004. (1950 pages) ISBN 978-0443073120
- Wikibook
  - physics of nuclear medicine (http://en.wikibooks.org/wiki/Basic_Physics_of_Nuclear_Medicine|Basic)

External links

- International Atomic Energy Agency (IAEA), Division of Human Health, Nuclear Medicine (http://www-naweb.iaea.org/nahu/nm/default.asp)
- RADAR Medical Procedure Radiation Dose Calculator and Consent Language Generator (http://www.doseinfo-radar.com/RADARDoseRiskCalc.html)
- Society of Nuclear Medicine (http://www.snm.org/)
  - Brochure: What is Nuclear Medicine? (http://interactive.snm.org/docs/whatisnucmed.pdf)
  - Resource center: information about nuclear medicine (http://interactive.snm.org/index.cfm?PageID=6309&RPID=1089)

Radionuclide

A **radionuclide** is an atom with an unstable nucleus, which is a nucleus characterized by excess energy which is available to be imparted either to a newly-created radiation particle within the nucleus, or else to an atomic electron (see internal conversion) . The radionuclide, in this process, undergoes radioactive decay, and emits a gamma ray(s) and/or subatomic particles. These particles constitute ionizing radiation. Radionuclides may occur naturally, but can also be artificially produced.

Radionuclides are often referred to by chemists and physicists as radioactive isotopes or **radioisotopes**, and play an important part in the technologies that provide us with food, water and good health. However, they can also constitute real or perceived dangers.

Origin

Naturally occurring radionuclides fall into three categories: primordial radionuclides, secondary radionuclides and cosmogenic radionuclides. Primordial radionuclides originate mainly from the interiors of stars and, like uranium and thorium, are still present because their half-lives are so long that they have not yet completely decayed. Secondary radionuclides are radiogenic isotopes derived from the decay of primordial radionuclides. They have shorter half-lives than primordial radionuclides. Cosmogenic isotopes, such as carbon-14, are present because they are continually being formed in the atmosphere due to cosmic rays.

Artificially produced radionuclides can be produced by nuclear reactors, particle accelerators or by radionuclide generators:

- Radioisotopes produced with nuclear reactors exploit the high flux of neutrons present. The neutrons activate elements placed within the reactor. A typical product from a nuclear reactor is thallium-201 and iridium-192. The elements that have a large propensity to take up the neutrons in the reactor have a high Barnes Number.
- Particle accelerators such as cyclotrons accelerate particles to bombard a target to produce radionuclides. Cyclotrons accelerate protons at a target to produce positron emitting radioisotopes e.g. fluorine-18.
- Radionuclide generators contain a parent isotope that decays to produce a radioisotope. The parent is usually produced in a nuclear reactor. A typical example is the technetium-99m generator used in nuclear medicine. The parent produced in the reactor is molybdenum-99.

Trace radionuclides are those that occur in tiny amounts in nature either due to inherent rarity, or to half-lives that are significantly shorter than the age of the Earth. Synthetic isotopes are inherently not naturally occurring on Earth, but can be created by nuclear reactions.

Uses

Radionuclides are used in two major ways: for their chemical properties and as sources of radiation. Radionuclides of familiar elements such as carbon can serve as tracers because they are chemically very similar to the non-radioactive nuclides, so most chemical, biological, and ecological processes treat them in a near identical way. One can then examine the result with a radiation detector, such as a geiger counter, to determine where

the provided atoms ended up. For example, one might culture plants in an environment in which the carbon dioxide contained radioactive carbon; then the parts of the plant that had laid down atmospheric carbon would be radioactive.

In nuclear medicine, radioisotopes are used for diagnosis, treatment, and research. Radioactive chemical tracers emitting gamma rays or positrons can provide diagnostic information about a person's internal anatomy and the functioning of specific organs. This is used in some forms of tomography: single photon emission computed tomography and positron emission tomography scanning.

Radioisotopes are also a promising method of treatment in hemopoietic forms of tumors, while the success for treatment of solid tumors has been limited so far. More powerful gamma sources sterilise syringes and other medical equipment. About one in two people in Western countries are likely to experience the benefits of nuclear medicine in their lifetime.

In biochemistry and genetics, radionuclides label molecules and allow tracing chemical and physiological processes occurring in living organisms, such as DNA replication or amino acid transport.

In food preservation, radiation is used to stop the sprouting of root crops after harvesting, to kill parasites and pests, and to control the ripening of stored fruit and vegetables.

In agriculture and animal husbandry, radionuclides also play an important role. They produce high intake of crops, disease and weather resistant varieties of crops, to study how fertilisers and insecticides work, and to improve the production and health of domestic animals.

Industrially, and in mining, radionuclides examine welds, to detect leaks, to study the rate of wear, erosion and corrosion of metals, and for on-stream analysis of a wide range of minerals and fuels.

Most household smoke detectors contain the radionuclide americium formed in nuclear reactors, saving many lives.

Radionuclides trace and analyze pollutants, to study the movement of surface water, and to measure water runoffs from rain and snow, as well as the flow rates of streams and rivers. Natural radionuclides are used in geology, archaeology, and paleontology to measure ages of rocks, minerals, and fossil materials.

Dangers

If radionuclides are released into the environment, through accident, poor disposal, or other means, they can potentially cause harmful effects of radioactive contamination. They can also cause damage if they are excessively used during treatment or in other ways applied to living beings. This is called radiation poisoning. Radionuclides can also cause malfunction of some electrical devices.

See also

- Hyperaccumulators table – 3
- Radioactivity in biology
- Radiometric dating
- Radionuclide cisternogram

References

- Carlsson J et al.:"Tumour therapy with radionuclides: assessment of progress and problems". *Radiotherapy and Oncology*, Volume 66, Issue 2, February 2003, Pages 107–117. PMID 12648782. Available online as full text.
- Radioisotopes in Industry [1], World Nuclear Association.

External links

- EPA - Radionuclides [2] - EPA's Radiation Protection Program: Information.
- Interactive Chart of Nuclides [3] - A chart of all nuclides

References

[1] http://world-nuclear.org/info/inf56.html
[2] http://www.epa.gov/rpdweb00/radionuclides/index.html
[3] http://www.nndc.bnl.gov/chart/

Advanced Experimental Techniques and Methods

Positron emission tomography

Positron emission tomography (**PET**) is a nuclear medicine imaging technique which produces a three-dimensional image or picture of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Images of tracer concentration in 3-dimensional space within the body are then reconstructed by computer analysis. In modern scanners, this reconstruction is often

Image of a typical positron emission tomography (PET) facility

accomplished with the aid of a CT X-ray scan performed on the patient during the same session, in the same machine.

If the biologically active molecule chosen for PET is FDG, an analogue of glucose, the concentrations of tracer imaged then give tissue metabolic activity, in terms of regional glucose uptake. Although use of this tracer results in the most common type of PET scan, other tracer molecules are used in PET to image the tissue concentration of many other types of molecules of interest.

Description

Operation

To conduct the scan, **a short-lived** radioactive tracer isotope, is injected into the living subject (usually into blood circulation). The tracer is chemically incorporated into a biologically active molecule. There is a waiting period while the active molecule becomes concentrated in tissues of interest; then the research subject or patient is placed in the imaging scanner. The

Schematic view of a detector block and ring of a PET scanner
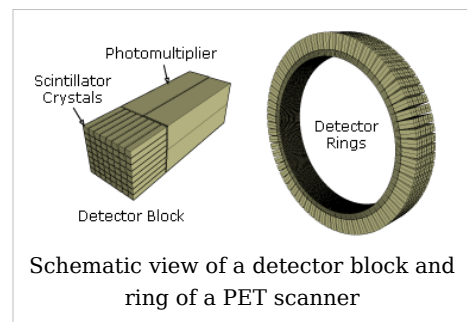
molecule most commonly used for this purpose is fluorodeoxyglucose (FDG), a sugar, for which the waiting period is typically an hour. During the scan a record of tissue concentration is made as the tracer decays.

As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, an antiparticle of the electron with opposite charge. After travelling up to a few millimeters the positron encounters and annihilates with an electron, producing a pair of annihilation (gamma) photons moving in opposite directions. These are detected when they reach a scintillator in the scanning device, creating a burst of light which is detected by photomultiplier tubes or silicon avalanche photodiodes (Si APD). The technique

Schema of a PET acquisition process

depends on simultaneous or coincident detection of the pair of photons moving in approximately opposite direction (it would be exactly opposite in their center of mass frame, but the scanner has no way to know this, and so has a built-in slight direction-error tolerance). Photons which do not arrive in temporal "pairs" (i.e. within a timing-window of few nanoseconds) are ignored.
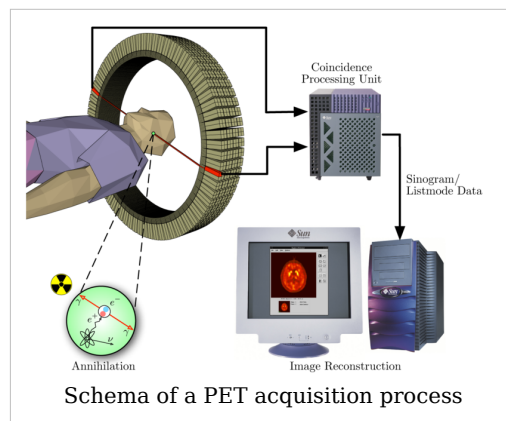
Localization of the positron annihilation event

The most significant fraction of electron-positron decays result in two 511 keV gamma photons being emitted at almost 180 degrees to each other; hence it is possible to localize their source along a straight line of coincidence (also called formally the **line of response** or **LOR**). In practice the LOR has a finite width as the emitted photons are not exactly 180 degrees apart. If the recovery time of detectors is about 1 picosecond rather than about 10 nanoseconds, it is possible to localize the event to a segment of a cord, whose length is determined by the detector timing resolution. As the timing resolution improves, the signal-to-noise ratio (SNR) of the image will improve, requiring fewer events to achieve the same image quality. This technology is not yet common, but it is available on some new systems [1].

Image reconstruction using coincidence statistics

More commonly, a technique much like the reconstruction of computed tomography (CT) and single photon emission computed tomography (SPECT) data is used, although the data set collected in PET is much poorer than CT, so reconstruction techniques are more difficult (see Image reconstruction of PET).

Using statistics collected from tens-of-thousands of coincidence events, a set of simultaneous equations for the total activity of each parcel of tissue along many LORs can be solved by a number of techniques, and thus a map of radioactivities as a function of location for parcels or bits of tissue (also called voxels), may be constructed and plotted. The resulting map shows the tissues in which the molecular probe has become concentrated, and can be interpreted by a nuclear medicine physician or radiologist in the context of the patient's diagnosis and treatment plan.
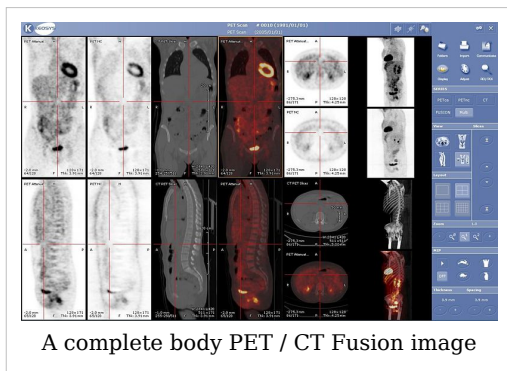
A complete body PET / CT Fusion image
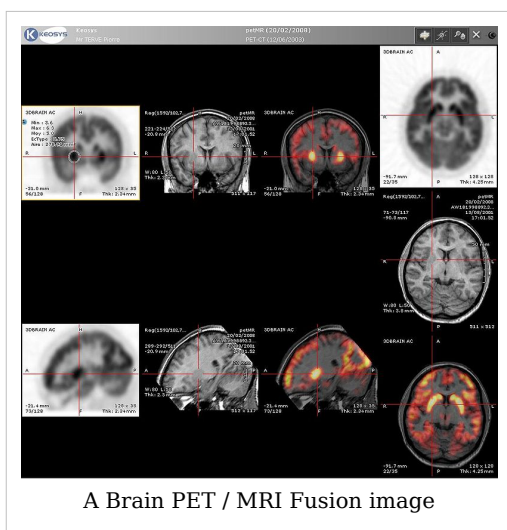
A Brain PET / MRI Fusion image

Combination of PET with CT and MRI

PET scans are increasingly read alongside CT or magnetic resonance imaging (MRI) scans, the combination ("co-registration") giving both anatomic and metabolic information (i.e., what the structure is, and what it is doing biochemically). Because PET imaging is most useful in combination with anatomical imaging, such as CT, modern PET scanners are now available with integrated high-end multi-detector-row CT scanners. Because the two scans can be performed in immediate sequence during the same session, with the patient not changing position between the two types of scans, the two sets of images are more-precisely registered, so that areas of abnormality on the PET imaging can be more perfectly correlated with anatomy on the CT images. This is very useful in showing detailed views of moving organs or structures with higher anatomical variation, which is more common outside the brain.

PET-MRI: At the Jülich Institute of Neurosciences and Biophysics, the world largest PET/MRI device will begin operation in April 2009: a 9.4-tesla magnetic resonance tomograph (MRT) combined with a positron emission tomograph (PET). Presently, only the head and brain can be imaged at these high magnetic field strengths. [2]

Radioisotopes

Radionuclides used in PET scanning are typically isotopes with short half lives such as carbon-11 (~20 min), nitrogen-13 (~10 min), oxygen-15 (~2 min), and fluorine-18 (~110 min). These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water or ammonia, or into molecules that bind to receptors or other sites of drug action. Such labelled compounds are known as radiotracers. It is important to recognize that PET technology can be used to trace the biologic pathway of any compound in living humans (and many other species as well), provided it can be radiolabeled with a PET isotope. Thus the specific processes that can be probed with PET are virtually limitless, and radiotracers for new target molecules and processes are being synthesized all the time; as of this writing there are already dozens in clinical use and hundreds applied in research. Due to the short half lives of most radioisotopes, the radiotracers must be produced using a cyclotron and radiochemistry laboratory that are in close proximity to the PET imaging facility. The half life of fluorine-18 is long enough such that fluorine-18 labeled radiotracers can be manufactured commercially at an offsite location.

Limitations

The minimization of radiation dose to the subject is an attractive feature of the use of short-lived radionuclides. Besides its established role as a diagnostic technique, PET has an expanding role as a method to assess the response to therapy, in particular, cancer therapy,[3] where the risk to the patient from lack of knowledge about disease progress is much greater than the risk from the test radiation.

Limitations to the widespread use of PET arise from the high costs of cyclotrons needed to produce the short-lived radionuclides for PET scanning and the need for specially adapted on-site chemical synthesis apparatus to produce the radiopharmaceuticals. Few hospitals and universities are capable of maintaining such systems, and most clinical PET is supported by third-party suppliers of radiotracers which can supply many sites simultaneously. This limitation restricts clinical PET primarily to the use of tracers labelled with F-18, which has a half life of 110 minutes and can be transported a reasonable distance before use, or to rubidium-82, which can be created in a portable generator and is used for myocardial perfusion studies. Nevertheless, in recent years a few on-site cyclotrons with integrated shielding and hot labs have begun to accompany PET units to remote hospitals. The presence of the small on-site cyclotron promises to expand in the future as the cyclotrons shrink in response to the high cost of isotope transportation to remote PET machines [4]

Because the half-life of F-18 is about two hours, the prepared dose of a radiopharmaceutical bearing this radionuclide will undergo multiple half-lives of decay during the working day. This necessitates frequent recalibration of the remaining dose (determination of activity per unit volume) and careful planning with respect to patient scheduling.

Image reconstruction

The raw data collected by a PET scanner are a list of 'coincidence events' representing near-simultaneous detection of annihilation photons by a pair of detectors. Each coincidence event represents a line in space connecting the two detectors along which the positron emission occurred. Modern systems with a high time resolution also use a technique (called "Time-of-flight") where they more precisely decide the difference in time between the detection of the two photons and can thus limit the length of the earlier mentioned line to around 10 cm.

Coincidence events can be grouped into projections images, called sinograms. The sinograms are sorted by the angle of each view and tilt, the latter in 3D case images. The sinogram images are analogous to the projections captured by computed tomography (CT) scanners, and can be reconstructed in a similar way. However, the statistics of the data is much worse than those obtained through transmission tomography. A normal PET data set has millions of counts for the whole acquisition, while the CT can reach a few billion counts. As such, PET data suffer from scatter and random events much more dramatically than CT data does.

In practice, considerable pre-processing of the data is required - correction for random coincidences, estimation and subtraction of scattered photons, detector dead-time correction (after the detection of a photon, the detector must "cool down" again) and detector-sensitivity correction (for both inherent detector sensitivity and changes in sensitivity due to angle of incidence).

Filtered back projection (FBP) has been frequently used to reconstruct images from the projections. This algorithm has the advantage of being simple while having a low requirement for computing resources. However, shot noise in the raw data is prominent in the reconstructed images and areas of high tracer uptake tend to form streaks across the image.

Iterative expectation-maximization algorithms are now the preferred method of reconstruction. The advantage is a better noise profile and resistance to the streak artifacts common with FBP, but the disadvantage is higher computer resource requirements.

Attenuation correction: As different LORs must traverse different thicknesses of tissue, the photons are attenuated differentially. The result is that structures deep in the body are reconstructed as having falsely low tracer uptake. Contemporary scanners can estimate attenuation using integrated x-ray CT equipment, however earlier equipment offered a crude form of CT using a gamma ray (positron emitting) source and the PET detectors.

While attenuation corrected images are generally more faithful representations, the correction process is itself susceptible to significant artifacts. As a result, both corrected and uncorrected images are always reconstructed and read together.

2D/3D reconstruction: Early PET scanners had only a single ring of detectors, hence the acquisition of data and subsequent reconstruction was restricted to a single transverse plane. More modern scanners now include multiple rings, essentially forming a cylinder of detectors.

There are two approaches to reconstructing data from such a scanner: 1) treat each ring as a separate entity, so that only coincidences within a ring are detected, the image from each ring can then be reconstructed individually (2D reconstruction), or 2) allow coincidences to be detected between rings as well as within rings, then reconstruct the entire volume together (3D).

3D techniques have better sensitivity (because more coincidences are detected and used) and therefore less noise, but are more sensitive to the effects of scatter and random coincidences, as well as requiring correspondingly greater computer resources. The advent of sub-nanosecond timing resolution detectors affords better random coincidence rejection, thus favoring 3D image reconstruction.

History

The concept of emission and transmission tomography was introduced by David Kuhl and Roy Edwards in the late 1950s. Their work later led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed by Michel Ter-Pogossian, Michael E. Phelps and others at the Washington University School of Medicine.[5] [6]

Work by Gordon Brownell, Charles Burnham and their associates at the Massachusetts General Hospital beginning in the 1950s contributed significantly to the development of PET technology and included the first demonstration of annihilation radiation for medical imaging[7] . Their innovations, including the use of light pipes, and volumetric analysis have been important in the deployment of PET imaging.

In the 1970s, Tatsuo Ido at the Brookhaven National Laboratory was the first to describe the synthesis of 18F-FDG, the most commonly used PET scanning isotope carrier. The compound was first administered to two normal human volunteers by Abass Alavi in August

1976 at the University of Pennsylvania. Brain images obtained with an ordinary (non-PET) nuclear scanner demonstrated the concentration of FDG in that organ. Later, the substance was used in dedicated positron tomographic scanners, to yield the modern procedure.

Applications

PET is both a medical and research tool. It is used heavily in clinical oncology (medical imaging of tumors and the search for metastases), and for clinical diagnosis of certain diffuse brain diseases such as those causing various types of dementias. PET is also an important research tool to map normal human brain and heart function.

PET is also used in pre-clinical studies using animals, where it allows repeated investigations into the same subjects. This is particularly valuable in cancer research, as it results in an increase in the statistical quality of the data (subjects can act as their own control) and substantially reduces the numbers of animals required for a given study.

Alternative methods of scanning include x-ray computed tomography (CT), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), ultrasound and single photon emission computed tomography (SPECT).

While some imaging scans such as CT and MRI isolate organic anatomic changes in the body, PET and SPECT are capable of detecting areas of molecular biology detail (even prior to anatomic change). PET scanning does this using radiolabelled molecular probes that have different rates of uptake depending on the type and function of tissue involved. Changing of regional blood flow in various anatomic structures (as a measure of the injected positron emitter) can be visualized and relatively quantified with a PET scan.

Maximum intensity projection (MIP) of a F-18 FDG wholebody PET acquisition, showing abnormal focal uptake in the liver. Normal isotope levels are seen in the brain, renal collection systems, and bladder. Image is rotating clockwise.

PET imaging is best performed using a dedicated PET scanner. However, it is possible to acquire PET images using a conventional dual-head gamma camera fitted with a coincidence detector. The quality of gamma-camera PET is considerably lower, and acquisition is slower. However, for institutions with low demand for PET, this may allow on-site imaging, instead of referring patients to another center, or relying on a visit by a mobile scanner.

PET is a valuable technique for some diseases and disorders, because it is possible to target the radio-chemicals used for particular bodily functions.

1. Oncology: PET scanning with the tracer fluorine-18 (F-18) fluorodeoxyglucose (FDG), called FDG-PET, is widely used in clinical oncology. This tracer is a glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase (whose mitochondrial form is greatly elevated in rapidly-growing malignant tumours). A typical dose of FDG used in an oncological scan is 200-400 MBq for an adult human. Because the oxygen

atom which is replaced by F-18 to generate FDG is required for the next step in glucose metabolism in all cells, no further reactions occur in FDG. Furthermore, most tissues (with the notable exception of liver and kidneys) cannot remove the phosphate added by hexokinase. This means that FDG is trapped in any cell which takes it up, until it decays, since phosphorylated sugars, due to their ionic charge, cannot exit from the cell. This results in intense radiolabeling of tissues with high glucose uptake, such as the brain, the liver, and most cancers. As a result, FDG-PET can be used for diagnosis, staging, and monitoring treatment of cancers, particularly in Hodgkin's disease, non Hodgkin's lymphoma, and lung cancer. Many other types of solid tumors will be found to be very highly labeled on a case-by-case basis-- a fact which becomes especially useful in searching for tumor metastasis, or for recurrence after a known highly-active primary tumor is removed. Because individual PET scans are more expensive than "conventional" imaging with computed tomography (CT) and magnetic resonance imaging (MRI), expansion of FDG-PET in cost-constrained health services will depend on proper health technology assessment; this problem is a difficult one because structural and functional imaging often cannot be directly compared, as they provide different information. Oncology scans using FDG make up over 90% of all PET scans in current practice.

Neurology: PET neuroimaging is based on an assumption that areas of high radioactivity are associated with brain activity. What is actually measured indirectly is the flow of blood to different parts of the brain, which is generally believed to be correlated, and has been measured using the tracer oxygen-15. However, because of its 2-minute half-life O-15 must be piped directly from a medical cyclotron for such uses, and this is difficult. In practice, since the brain is normally a rapid user of glucose, and since brain pathologies such as Alzheimer's disease greatly decrease brain metabolism of both glucose and oxygen in tandem, standard FDG-PET of the brain, which measures regional glucose use, may also be

PET scan of the human brain.

successfully used to differentiate Alzheimer's disease from other dementing processes, and also to make early diagnosis of Alzheimer's disease. The advantage of FDG-PET for these uses is its much wider availability. PET imaging with FDG can also be used for localization of seizure focus: A seizure focus will appear as hypometabolic during an interictal scan. Several radiotracers (i.e. radioligands) have been developed for PET that are ligands for specific neuroreceptor subtypes such as [^{11}C] raclopride and [^{18}F] fallypride for dopamine D2/D3 receptors, [^{11}C]McN 5652 and [^{11}C]DASB for serotonin transporters, or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme). These agents permit the visualization of neuroreceptor pools in the context of a plurality of neuropsychiatric and neurologic illnesses. A novel probe developed at the University of Pittsburgh termed PIB (Pittsburgh Compound-B) permits the visualization of amyloid plaques in the brains of Alzheimer's patients. This technology could assist clinicians in making a positive clinical diagnosis of AD pre-mortem and aid in the development of novel anti-amyloid therapies.

3. Cardiology, atherosclerosis and vascular disease study: In clinical cardiology, FDG-PET can identify so-called "hibernating myocardium", but its cost-effectiveness in this role versus SPECT is unclear. Recently, a role has been suggested for FDG-PET imaging of atherosclerosis to detect patients at risk of stroke [8].

4. Neuropsychology / Cognitive neuroscience: To examine links between specific psychological processes or disorders and brain activity.

5. Psychiatry: Numerous compounds that bind selectively to neuroreceptors of interest in biological psychiatry have been radiolabeled with C-11 or F-18. Radioligands that bind to dopamine receptors (D1,D2, reuptake transporter), serotonin receptors (5HT1A, 5HT2A, reuptake transporter) opioid receptors (mu) and other sites have been used successfully in studies with human subjects. Studies have been performed examining the state of these receptors in patients compared to healthy controls in schizophrenia, substance abuse, mood disorders and other psychiatric conditions.

6. Pharmacology: In pre-clinical trials, it is possible to radiolabel a new drug and inject it into animals. Such scans are referred to as biodistribution studies. The uptake of the drug, the tissues in which it concentrates, and its eventual elimination, can be monitored far more quickly and cost effectively than the older technique of killing and dissecting the animals to discover the same information. Much more commonly, however, drug occupancy at a purported site of action can be inferred indirectly by competition studies between unlabeled drug and radiolabeled compounds known apriori to bind with specificity to the site. A single radioligand can be used this way to test many potential drug candidates for the same target. A related technique involves scanning with radioligands that compete with an endogenous (naturally occurring) substance at a given receptor to demonstrate that a drug causes the release of the natural substance.

7. PET technology for small animal imaging: A miniature PET tomograph has been constructed that is small enough for a fully conscious and mobile rat to wear on its head while walking around [9]. This RatCAP (Rat Conscious Animal PET) allows animals to be scanned without the confounding effects of anesthesia. PET scanners designed specifically for imaging rodents microPET or other scanners for small primates are marketed for academic and pharmaceutical research.

Safety

PET scanning is non-invasive, but it does involve exposure to ionizing radiation. The total dose of radiation is small, however, usually around 7 mSv. This can be compared to 2.2 mSv average annual background radiation in the UK, 0.02 mSv for a chest x-ray, up to 8 mSv for a CT scan of the chest, according to the UK National Radiological Protection Board.[10] A policy change suggested by the IFALPA member associations in year 1999 mentioned that an aircrew member is likely to receive a radiation dose of 4-9 mSv per year.[11]

See also

- Diffuse optical imaging
- Hot cell (Equipment used to produce the radiopharmaceuticals used in PET)
- Molecular Imaging

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External links

- PET Images (http://rad.usuhs.edu/medpix/master.php3?mode=image_finder&
  action=search&srchstr=&srch_type=all&labels=&details=2&no_filter=2&
  plane_id=&capt_id=-4&filter_m=modality&filter_o=&acr_pre=&filter_p=&
  acr_post=#top) Search MedPix(r)
- Seeing is believing: In vivo functional real-time imaging of transplanted islets using
  positron emission tomography (PET)(a protocol) (http://www.natureprotocols.com/
  2006/12/21/seeing_is_believing_in_vivo_fu_1.php)
- The nuclear medicine and molecular medicine podcast (http://nuccast.com) - Podcast
- Positron emmission particle tracking (http://www.np.ph.bham.ac.uk/pic/pept.htm)
  (PEPT) - engineering analysis tool based on PET that is able to track single particles in
  3D within mixing systems or fluidised beds. Developed at the University of Birmingham,
  UK.
- CMS coverage of PET scans (http://www.hematologytimes.com/ht/p_article.
  do?id=948)

2D-FT NMRI and Spectroscopy

2D-FT Nuclear magnetic resonance imaging (**2D-FT NMRI**), or **Two-dimensional Fourier transform** nuclear magnetic resonance imaging (**NMRI**), is primarily a non—invasive imaging technique most commonly used in biomedical research and medical radiology/nuclear medicine/MRI to visualize structures and functions of the living systems and single cells. For example it can provides fairly detailed images of a human body in any selected cross-sectional plane, such as longitudinal, transversal, sagital, etc. The basic NMR phenomenon or physical principle[1] is essentially the same in N(MRI), nuclear magnetic resonance/FT (NMR) spectroscopy, topical NMR, or even in Electron Spin Resonance /EPR; however, the details are significantly different at present for EPR, as only in the early days of NMR the static magnetic field was scanned for obtaining spectra, as it is still the case in many EPR or ESR spectrometers. NMRI, on the other hand, often utilizes a linear magnetic field gradient to obtain an image that combines the visualization of molecular structure and dynamics. It is this dynamic aspect of NMRI, as well as its highest sensitivity for the ^{1}H nucleus that distinguishes it very dramatically from X-ray CAT scanning that 'misses' hydrogens because of their very low X-ray scattering factor.

Thus, NMRI provides much greater contrast especially for the different soft tissues of the body than computed tomography (CT) as its most sensitive option observes the nuclear spin distribution and dynamics of highly mobile molecules that contain the naturally abundant, stable hydrogen isotope ^{1}H as in plasma water molecules, blood, disolved metabolites and fats. This approach makes it most useful in cardiovascular, oncological (cancer), neurological (brain), musculoskeletal, and cartilage imaging. Unlike CT, it uses no ionizing radiation, and also unlike nuclear imaging it does not employ any radioactive isotopes. Some of the first MRI images reported were published in 1973[2] and the first study performed on a human took place on July 3, 1977.[3] Earlier papers were also published by Sir Peter Mansfield[4] in UK (Nobel Laureate in 2003), and R. Damadian in the USA[5] , (together with an approved patent for 'fonar', or magnetic imaging). The detailed physical theory of NMRI was published by Peter Mansfield in 1973[6] . Unpublished 'high-resolution' (50 micron resolution) images of other living systems, such as hydrated wheat grains, were

also obtained and communicated in UK in 1977-1979, and were subsequently confirmed by articles published in *Nature* by Peter Callaghan.

NMR Principle

Certain nuclei such as ^{1}H nuclei, or `fermions' have spin-1/2, because there are two spin states, referred to as "up" and "down" states. The nuclear magnetic resonance absorption phenomenon occurs when samples containing such nuclear spins are placed in a static magnetic field and a very short radiofrequency pulse is applied with a center, or carrier, frequency matching that of the transition between the up and down states of the spin-1/2 ^{1}H nuclei that were polarized by the static magnetic field. [7] Very low field schemes have also been recently reported.[8]

Advanced 4.7 T clinical diagnostics and biomedical research NMR Imaging instrument.

Chemical Shifts

NMR is a very useful family of techniques for chemical and biochemical research because of the chemical shift; this effect consists in a frequency shift of the nuclear magnetic resonance for specific chemical groups or atoms as a result of the partial shielding of the corresponding nuclei from the applied, static external magnetic field by the electron orbitals (or molecular orbitals) surrounding such nuclei present in the chemical groups. Thus, the higher the electron density surrounding a specific nucleus the larger the chemical shift will be. The resulting magnetic field at the nucleus is thus lower than the applied external magnetic field and the resonance frequencies observed as a result of such shielding are lower than the value that would be observed in the absence of any electronic orbital shielding. Furthermore, in order to obtain a chemical shift value independent of the strength of the applied magnetic field and allow for the direct comparison of spectra obtained at different magnetic field values, the chemical shift is defined by the ratio of the strength of the local magnetic field value at the observed (electron orbital-shielded) nucleus by the external magnetic field strength, $\mathbf{H}_{loc}/ \mathbf{H}_0$. The first NMR observations of the chemical shift, with the correct physical chemistry interpretation, were reported for ^{19}F containing compounds in the early 1950s by Herbert S. Gutowsky and Charles P. Slichter from the University of Illinois at Urbana (USA).

A related effect in metals is called the Knight shift, which is due only to the conduction electrons. Such conduction electrons present in metals induce an "additional" local field at the nuclear site, due to the spin re-orientation of the conduction electrons in the presence of the applied (constant), external magnetic field. This is only broadly `similar' to the

chemical shift in either solutions or diamagnetic solids.

NMR Imaging Principles

A number of methods have been devised for combining magnetic field gradients and radiofrequency pulsed excitation to obtain an image. Two major maethods involve either 2D -FT or 3D-FT[9] reconstruction from projections, somewhat similar to Computed Tomography, with the exception of the image interpretation that in the former case must include dynamic and relaxation/contrast enhancement information as well. Other schemes involve building the NMR image either point-by-point or line-by-line. Some schemes use instead gradients in the rf field rather than in the static magnetic field. The majority of NMR images routinely obtained are either by the Two-Dimensional Fourier Transform (2D-FT) technique [10] (with slice selection), or by the Three-Dimensional Fourier Transform (3D—FT) techniques that are however much more time consuming at present. 2D-FT NMRI is sometime called in common parlance a "spin-warp". An NMR image corresponds to a spectrum consisting of a number of `spatial frequencies' at different locations in the sample investigated, or in a patient.[11] A two–dimensional Fourier transformation of such a "real" image may be considered as a representation of such "real waves" by a matrix of spatial frequencies known as the k–space. We shall see next in some mathematical detail how the 2D-FT computation works to obtain 2D-FT NMR images.

Two-dimensional Fourier transform imaging and spectroscopy

A two-dimensional Fourier transform (2D-FT) is computed numerically or carried out in two stages, both involving `standard', one-dimensional Fourier transforms. However, the second stage Fourier transform is not the inverse Fourier transform (which would result in the original function that was transformed at the first stage), but a Fourier transform in a second variable—which is `shifted' in value—relative to that involved in the result of the first Fourier transform. Such 2D-FT analysis is a very powerful method for both NMRI and two-dimensional nuclear magnetic resonance spectroscopy (2D-FT NMRS)[12] that allows the three-dimensional reconstruction of polymer and biopolymer structures at atomic resolution.[13] for molecular weights (Mw) of dissolved biopolymers in aqueous solutions (for example) up to about 50,000 Mw. For larger biopolymers or polymers, more complex methods have been developed to obtain limited structural resolution needed for partial 3D-reconstructions of higher molecular structures, e.g. for up 900,000 Mw or even oriented microcrystals in aqueous suspensions or single crystals; such methods have also been reported for *in vivo* 2D-FT NMR spectroscopic studies of algae, bacteria, yeast and certain mammalian cells, including human ones. The 2D-FT method is also widely utilized in optical spectroscopy, such as *2D-FT NIR hyperspectral imaging* (2D-FT NIR-HS), or in MRI imaging for research and clinical, diagnostic applications in Medicine. In the latter case, 2D-FT NIR-HS has recently allowed the identification of single, malignant cancer cells surrounded by healthy human breast tissue at about 1 micron resolution, well-beyond the resolution obtainable by 2D-FT NMRI for such systems in the limited time available for such diagnostic investigations (and also in magnetic fields up to the FDA approved magnetic field strength $\mathbf{H}_0$ of 4.7 T, as shown in the top image of the state-of-the-art NMRI instrument). A more precise mathematical definition of the `double' (2D) Fourier transform involved in both 2D NMRI and 2D-FT NMRS is specified next, and a precise example

follows this generally accepted definition.

2D-FT Definition

A *2D-FT, or two-dimensional Fourier transform*, is a standard Fourier transformation of a function of two variables, $\mathbf{f}(x_1, x_2)$, carried first in the first variable x_1, followed by the Fourier transform in the second variable x_2 of the resulting function $\mathbf{F}(s_1, x_2)$. Note that in the case of both 2D-FT NMRI and 2D-FT NMRS the two independent variables in this definition are in the time domain, whereas the results of the two successive Fourier transforms have, of course, frequencies as the independent variable in the NMRS, and ultimately spatial coordinates for both 2D NMRI and 2D-FT NMRS following computer structural recontructions based on special algorithms that are different from FT or 2D-FT. Moreover, such structural algorithms are different for 2D NMRI and 2D-FT NMRS: in the former case they involve macroscopic, or anatomical structure detrmination, whereas in the latter case of 2D-FT NMRS the atomic structure reconstruction algorithms are based on the quantum theory of a microphysical (quantum) process such as nuclear Overhauser enhancement NOE, or specific magnetic dipole-dipole interactions[14] between neighbor nuclei.

Example 1

A 2D Fourier transformation and phase correction is applied to a set of 2D NMR (FID) signals: $\mathbf{s}(t_1, t_2)$ yielding a real 2D-FT NMR `spectrum' (collection of 1D FT-NMR spectra) represented by a matrix $\mathbf{S}$ whose elements are

$$\mathbf{S}\,(\nu_1, \nu_2) = \mathbf{Re} \int \int cos(\nu_1 t_1) exp^{(-i\nu_2 t_2)} s(t_1, t_2) dt_1 dt_2$$

where : ν_1 and : ν_2 denote the discrete indirect double-quantum and single-quantum(detection) axes, respectively, in the 2D NMR experiments. Next, the *covariance matrix* is calculated in the frequency domain according to the following equation

$$\mathbf{C}\quad (\nu_2', \nu_2) = S^T S = \sum_{\nu^1}[S(\nu_1, \nu_2')S(\nu_1, \nu_2)],$$ with : ν_2, ν_2' taking all possible single-quantum frequency values and with the summation carried out over all discrete, double quantum frequencies : ν_1.

Example 2

Atomic Structure from 2D-FT STEM Images [15] of electron distributions in a high-temperature cuprate superconductor `paracrystal' reveal both the domains (or `location') and the local symmetry of the 'pseudo-gap' in the electron-pair correlation band responsible for the high—temperature superconductivity effect (obtained at Cornell University). So far there have been three Nobel prizes awarded for 2D-FT NMR/MRI during 1992-2003, and an additional, earlier Nobel prize for 2D-FT of X-ray data (`CAT scans'); recently the advanced possibilities of 2D-FT techniques in Chemistry, Physiology and Medicine [16] received very significant recognition.[17]

Brief explanation of NMRI diagnostic uses in Pathology

As an example, a diseased tissue such as a malign tumor, can be detected by 2D-FT NMRI because the hydrogen nuclei of molecules in different tissues return to their equilibrium spin state at different relaxation rates, and also because of the manner in which a malign tumor spreads and grows rapidly along the blood vessels adjacent to the tumor, also inducing further vascularization to occur. By changing the pulse delays in the RF pulse sequence employed, and/or the RF pulse sequence itself, one may obtain a `relaxation—based contrast', or contrast enhancement between different types of body tissue, such as normal vs. diseased tissue cells for example. Excluded from such diagnostic observations by NMRI are all patients with ferromagnetic metal implants, (e.g., cochlear implants), and all cardiac pacemaker patients who cannot undergo any NMRI scan because of the very intense magnetic and RF fields employed in NMRI which would strongly interfere with the correct functioning of such pacemakers. It is, however, conceivable that future developments may also include along with the NMRI diagnostic treatments with special techniques involving applied magnetic fields and very high frequency RF. Already, surgery with special tools is being experimented on in the presence of NMR imaging of subjects.Thus, NMRI is used to image almost every part of the body, and is especially useful for diagnosis in neurological conditions, disorders of the muscles and joints, for evaluating tumors, such as in lung or skin cancers, abnormalities in the heart (especially in children with hereditary disorders), blood vessels, CAD, atherosclerosis and cardiac infarcts [18] (courtesy of Dr. Robert R. Edelman)

See also

- Nuclear magnetic resonance (NMR)
- Edward Mills Purcell
- Felix Bloch
- Medical imaging
- Paul C. Lauterbur
- Magnetic resonance microscopy
- Peter Mansfield
- Computed tomography (CT)

- Solid-state NMR
- Knight shift
- John Hasbrouck Van Vleck
- Chemical shift
- Herbert S. Gutowsky
- John S. Waugh
- Charles Pence Slichter
- Protein nuclear magnetic resonance spectroscopy
- Kurt Wüthrich
- Nuclear Overhauser effect
- Fourier transform spectroscopy(FTS)
- Jean Jeneer
- Richard R. Ernst

- FT-NIRS (NIR)
- Magnetic resonance elastography

- Relaxation
- Earth's field NMR (EFNMR)
- Robinson oscillator

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gov/articlerender.fcgi?tool=pmcentrez&artid=15521). http://www.pnas.org/cgi/
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External links

- Cardiac Infarct or "heart attack" Imaged in Real Time by 2D-FT NMRI (http://www.
  mr-tip.com/exam_gifs/cardiac_infarct_short_axis_cine_6.gif)
- Interactive Flash Animation on MRI (http://www.e-mri.org) - *Online Magnetic
  Resonance Imaging physics and technique course*
- Herbert S. Gutowsky
- Jiri Jonas and Charles P. Slichter: NMR Memoires at NAS about Herbert Sander
  Gutowsky; NAS = National Academy of Sciences, USA, (http://books.nap.edu/html/
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- 3D Animation Movie about MRI Exam (http://www.patiencys.com/MRI/)
- International Society for Magnetic Resonance in Medicine (http://www.ismrm.org)
- Danger of objects flying into the scanner (http://www.simplyphysics.com/
  flying_objects.html)

Related Wikipedia websites

- Medical imaging
- Computed tomography
- Magnetic resonance microscopy
- Fourier transform spectroscopy
- FT-NIRS
- Chemical imaging
- Magnetic resonance elastography

- Nuclear magnetic resonance (NMR)
- Chemical shift
- Relaxation
- Robinson oscillator
- Earth's field NMR (EFNMR)
- Rabi cycle

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NMR spectroscopy

Nuclear magnetic resonance spectroscopy, most commonly known as **NMR spectroscopy**, is the name given to a technique which exploits the magnetic properties of certain nuclei. This phenomenon and its origins are detailed in a separate section on nuclear magnetic resonance. The most important applications for the organic chemist are proton NMR and carbon-13 NMR spectroscopy. In principle, NMR is applicable to any nucleus possessing spin.

Many types of information can be obtained from an NMR spectrum. Much like using infrared spectroscopy to identify functional groups, analysis of a 1D NMR spectrum provides information on the number and type of chemical entities in a molecule. However, NMR provides much more information than IR.

A 900MHz NMR instrument with a 21.2 T magnet at HWB-NMR, Birmingham, UK, being loaded with a sample.

The impact of NMR spectroscopy on the natural sciences has been substantial. It can, among other things, be used to study mixtures of analytes, to understand dynamic effects such as change in temperature and reaction mechanisms, and is an invaluable tool in understanding protein and nucleic acid structure and function. It can be applied to a wide variety of samples, both in the solution and the solid state.

Basic NMR techniques

When placed in a magnetic field, NMR active nuclei (such as ^{1}H or ^{13}C) absorb at a frequency characteristic of the isotope. The resonant frequency, energy of the absorption and the intensity of the signal are proportional to the strength of the magnetic field. For example, in a 21 tesla magnetic field, protons resonate at 900 MHz. It is common to refer to a 21 T magnet as a 900 MHz magnet, although different nuclei resonate at a different frequency at this field strength.

In the Earth's magnetic field the same nuclei resonate at audio frequencies. This effect is used in Earth's field NMR spectrometers and other instruments. Because these instruments are portable and inexpensive, they are often used for teaching and field work.
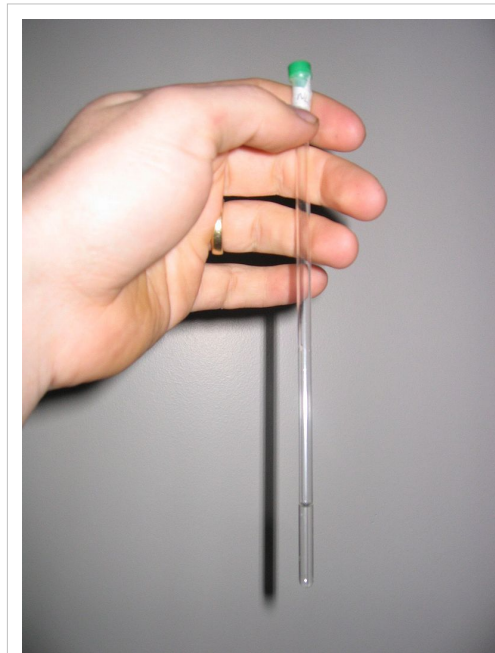
The NMR sample is prepared in a thin-walled glass tube - an NMR tube.

Chemical shift

Depending on the local chemical environment, different protons in a molecule resonate at slightly different frequencies. Since both this frequency shift and the fundamental resonant frequency are directly proportional to the strength of the magnetic field, the shift is converted into a *field-independent* dimensionless value known as the chemical shift. The chemical shift is reported as a relative measure from some reference resonance frequency. (For the nuclei ^{1}H, ^{13}C, and ^{29}Si, TMS (tetramethylsilane) is commonly used as a reference.) This difference between the frequency of the signal and the frequency of the reference is divided by frequency of the reference signal to give the chemical shift. The frequency shifts are extremely small in comparison to the fundamental NMR frequency. A typical frequency shift might be 100 Hz, compared to a fundamental NMR frequency of 100 MHz, so the chemical shift is generally expressed in parts per million (ppm).[1]

By understanding different chemical environments, the chemical shift can be used to obtain some structural information about the molecule in a sample. The conversion of the raw data to this information is called *assigning* the spectrum. For example, for the ^{1}H-NMR spectrum for ethanol (CH_3CH_2OH), one would expect three specific signals at three specific chemical shifts: one for the C*H*$_3$ group, one for the C*H*$_2$ group and one for the O*H* group. A typical CH$_3$ group has a shift around 1 ppm, a CH$_2$ attached to an OH has a shift of around 4 ppm and an OH has a shift around 2–3 ppm depending on the solvent used.

Because of molecular motion at room temperature, the three methyl protons *average* out during the course of the NMR experiment (which typically requires a few ms). These protons become degenerate and form a peak at the same chemical shift.

The shape and size of peaks are indicators of chemical structure too. In the example above—the proton spectrum of ethanol—the CH$_3$ peak would be three times as large as the OH. Similarly the CH$_2$ peak would be twice the size of the OH peak but only 2/3 the size of the CH$_3$ peak.

Modern analysis software allows analysis of the size of peaks to understand how many protons give rise to the peak. This is known as integration—a mathematical process which calculates the area under a graph (essentially what a spectrum is). The analyst must integrate the peak and not measure its height because the peaks also have *width*—and thus its size is dependent on its area not its height. However, it should be mentioned that the number of protons, or any other observed nucleus, is only proportional to the intensity, or the integral, of the NMR signal, in the very simplest one-dimensional NMR experiments. In more elaborate experiments, for instance, experiments typically used to obtain carbon-13 NMR spectra, the integral of the signals depends on the relaxation rate of the nucleus, and its scalar and dipolar coupling constants. Very often these factors are poorly understood - therefore, the integral of the NMR signal is very difficult to interpret in more complicated NMR experiments.

J-coupling

Multiplicity	Intensity Ratio
Singlet (s)	1
Doublet (d)	1:1
Triplet (t)	1:2:1
Quartet (q)	1:3:3:1
Quintet	1:4:6:4:1
Sextet	1:5:10:10:5:1
Septet	1:6:15:20:15:6:1

Some of the most useful information for structure determination in a one-dimensional NMR spectrum comes from **J-coupling** or **scalar coupling** (a special case of spin-spin coupling) between NMR active nuclei. This coupling arises from the interaction of different spin states through the chemical bonds of a molecule and results in the splitting of NMR signals. These splitting patterns can be complex or simple and, likewise, can be straightforwardly interpretable or deceptive. This coupling provides detailed insight into the connectivity of atoms in a molecule.

Coupling to *n* equivalent (spin ½) nuclei splits the signal into a *n*+1 **multiplet** with intensity ratios following Pascal's triangle as described on the right. Coupling to additional spins will lead to further splittings of each component of the multiplet e.g. coupling to two different spin ½ nuclei with significantly different coupling constants will lead to a *doublet of doublets* (abbreviation: dd). Note that coupling between nuclei that are chemically equivalent (that is, have the same chemical shift) has no effect of the NMR spectra and couplings between nuclei that are distant (usually more than 3 bonds apart for protons in flexible molecules) are usually too small to cause observable splittings. *Long-range* couplings over more than three bonds can often be observed in cyclic and aromatic compounds, leading to more complex splitting patterns.

For example, in the proton spectrum for ethanol described above, the CH_3 group is split into a *triplet* with an intensity ratio of 1:2:1 by the two neighboring CH_2 protons. Similarly, the CH_2 is split into a *quartet* with an intensity ratio of 1:3:3:1 by the three neighboring CH_3 protons. In principle, the two CH_2 protons would also be split again into a *doublet* to form a *doublet of quartets* by the hydroxyl proton, but intermolecular exchange of the

acidic hydroxyl proton often results in a loss of coupling information.

Coupling to any spin ½ nuclei such as phosphorus-31 or fluorine-19 works in this fashion (although the magnitudes of the coupling constants may be very different). But the splitting patterns differ from those described above for nuclei with spin greater than ½ because the spin quantum number has more than two possible values. For instance, coupling to deuterium (a spin 1 nucleus) splits the signal into a *1:1:1 triplet* because the spin 1 has three spin states. Similarly, a spin 3/2 nucleus splits a signal into a *1:1:1:1 quartet* and so on.

Coupling combined with the chemical shift (and the integration for protons) tells us not only about the chemical environment of the nuclei, but also the number of *neighboring* NMR active nuclei within the molecule. In more complex spectra with multiple peaks at similar chemical shifts or in spectra of nuclei other than hydrogen, coupling is often the only way to distinguish different nuclei.

Second-order (or strong) coupling

The above description assumes that the coupling constant is small in comparison with the difference in NMR frequencies between the inequivalent spins. If the shift separation decreases (or the coupling strength increases), the multiplet intensity patterns are first distorted, and then become more complex and less easily analyzed (especially if more than two spins are involved). Intensification of some peaks in a multiplet is achieved at the expense of the remainder, which sometimes almost disappear in the background noise, although the integrated area under the peaks remains constant. In most high-field NMR, however, the distortions are usually modest and the characteristic distortions (*roofing*) can in fact help to identify related peaks.

Second-order effects decrease as the frequency difference between multiplets increases, so that high-field (i.e. high-frequency) NMR spectra display less distortion than lower frequency spectra. Early spectra at 60 MHz were more prone to distortion than spectra from later machines typically operating at frequencies at 200 MHz or above.

Magnetic inequivalence

More subtle effects can occur if chemically equivalent spins (i.e. nuclei related by symmetry and so having the same NMR frequency) have different coupling relationships to external spins. Spins that are chemically equivalent but are not indistinguishable (based on their coupling relationships) are termed magnetically inequivalent. For example, the 4 H sites of 1,2-dichlorobenzene divide into two chemically equivalent pairs by symmetry, but an individual member of one of the pairs has different couplings to the spins making up the other pair. Magnetic inequivalence can lead to highly complex spectra which can only be analyzed by computational modeling. Such effects are more common in NMR spectra of aromatic and other non-flexible systems, while conformational averaging about C-C bonds in flexible molecules tends to equalize the couplings between protons on adjacent carbons, reducing problems with magnetic inequivalence.

Correlation spectroscopy

Correlation spectroscopy is one of several types of two-dimensional nuclear magnetic resonance (NMR) spectroscopy. This type of NMR experiment is best known by its acronym, COSY. Other types of two-dimensional NMR include J-spectroscopy, exchange spectroscopy (EXSY), Nuclear Overhauser effect spectroscopy (NOESY), total correlation spectroscopy (TOCSY) and heteronuclear correlation experiments, such as HSQC, HMQC, and HMBC. Two-dimensional NMR spectra provide more information about a molecule than one-dimensional NMR spectra and are especially useful in determining the structure of a molecule, particularly for molecules that are too complicated to work with using one-dimensional NMR. The first two-dimensional experiment, COSY, was proposed by Jean Jeener, a professor at Université Libre de Bruxelles, in 1971. This experiment was later implemented by Walter P. Aue, Enrico Bartholdi and Richard R. Ernst, who published their work in 1976.[2]

Solid-state nuclear magnetic resonance

A variety of physical circumstances does not allow molecules to be studied in solution, and at the same time not by other spectroscopic techniques to an atomic level, either. In solid-phase media, such as crystals, microcrystalline powders, gels, anisotropic solutions, etc., it is in particular the dipolar coupling and chemical shift anisotropy that become dominant to the behaviour of the nuclear spin systems. In conventional solution-state NMR spectroscopy, these additional interactions would lead to a significant broadening of spectral lines. A variety of techniques allows to establish high-resolution conditions, that can, at least for ^{13}C spectra, be comparable to solution-state NMR spectra.

Two important concepts for high-resolution solid-state NMR spectroscopy are the limitation of possible molecular orientation by sample orientation, and the reduction of anisotropic nuclear magnetic interactions by sample spinning. Of the latter approach, fast spinning around the magic angle is a very prominent method, when the system comprises spin 1/2 nuclei. A number of intermediate techniques, with samples of partial alignment or reduced mobility, is currently being used in NMR spectroscopy.

Applications in which solid-state NMR effects occur are often related to structure investigations on membrane proteins, protein fibrils or all kinds of polymers, and chemical analysis in inorganic chemistry, but also include "exotic" applications like the plant leaves and fuel cells.

NMR spectroscopy applied to proteins

Much of the recent innovation within NMR spectroscopy has been within the field of protein NMR, which has become a very important technique in structural biology. One common goal of these investigations is to obtain high resolution 3-dimensional structures of the protein, similar to what can be achieved by X-ray crystallography. In contrast to X-ray crystallography, NMR is primarily limited to relatively small proteins, usually smaller than 35 kDa, though technical advances allow ever larger structures to be solved. NMR spectroscopy is often the only way to obtain high resolution information on partially or wholly intrinsically unstructured proteins.

Proteins are orders of magnitude larger than the small organic molecules discussed earlier in this article, but the same NMR theory applies. Because of the increased number of each

element present in the molecule, the basic 1D spectra become crowded with overlapping signals to an extent where analysis is impossible. Therefore, multidimensional (2, 3 or 4D) experiments have been devised to deal with this problem. To facilitate these experiments, it is desirable to isotopically label the protein with ^{13}C and ^{15}N because the predominant naturally occurring isotope ^{12}C is not NMR-active, whereas the nuclear quadrupole moment of the predominant naturally occurring ^{14}N isotope prevents high resolution information to be obtained from this nitrogen isotope. The most important method used for structure determination of proteins utilizes NOE experiments to measure distances between pairs of atoms within the molecule. Subsequently, the obtained distances are used to generate a 3D structure of the molecule using a computer program.

See also

- In vivo magnetic resonance spectroscopy
- Low field NMR
- Magnetic Resonance Imaging
- Nuclear Magnetic Resonance
- NMR spectra database
- NMR tube - includes sample preparation
- Protein nuclear magnetic resonance spectroscopy

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External links

- Protein NMR- A Practical Guide (http://www.protein-nmr.org.uk) Practical guide to NMR, in particular protein NMR assignment
- James Keeler. http://www-keeler.ch.cam.ac.uk/lectures/Irvine/|"Understanding NMR Spectroscopy" (reprinted at University of Cambridge). University of California, Irvine. http://www-keeler.ch.cam.ac.uk/lectures/Irvine/. Retrieved on 2007-05-11.
- The Basics of NMR (http://www.cis.rit.edu/htbooks/nmr/) - A non-technical overview of NMR theory, equipment, and techniques by Dr. Joseph Hornak, Professor of Chemistry at RIT
- NMRWiki.ORG (http://nmrwiki.org) project, a Wiki dedicated to NMR, MRI, and EPR.
- NMR spectroscopy for organic chemistry (http://www.organicworldwide.net/nmr.html)
- The Spectral Game (http://spectralgame.com) NMR spectroscopy game.

Free NMR processing, analysis and simulation software

- WINDNMR-Pro (http://www.chem.wisc.edu/areas/reich/plt/windnmr.htm) - simulation software for interactive calculation of first and second-order spin-coupled multiplets and a variety of DNMR lineshapes.
- CARA (http://www.nmr.ch) - resonance assignment software developed at the Wüthrich group

- NMRShiftDB (http://www.nmrshiftdb.org) - open database and NMR prediction website
- Spinworks (http://www.umanitoba.ca/chemistry/nmr/spinworks/)

Fourier transform spectroscopy

Fourier transform spectroscopy is a measurement technique whereby spectra are collected based on measurements of the temporal coherence of a radiative source, using time-domain measurements of the electromagnetic radiation or other type of radiation. It can be applied to a variety of types of spectroscopy including optical spectroscopy, infrared spectroscopy (FT IR, FT-NIRS), Fourier transform (FT) nuclear magnetic resonance[1] , mass spectrometry and electron spin resonance spectroscopy. There are several methods for measuring the temporal coherence of the light, including the continuous wave *Michelson* or *Fourier transform* spectrometer and the pulsed Fourier transform spectrograph (which is more sensitive and has a much shorter sampling time than conventional spectroscopic techniques, but is only applicable in a laboratory environment).

Continuous wave *Michelson* or *Fourier transform* spectrograph

The Michelson spectrograph is similar to the instrument used in the Michelson-Morley experiment. Light from the source is split into two beams by a half-silvered mirror, one is reflected off a fixed mirror and one off a moving mirror which introduces a time delay -- the Fourier transform spectrometer is just a Michelson interferometer with a movable mirror. The beams interfere, allowing the temporal coherence of the light to be measured at each different time delay setting, effectively converting the time domain into a spatial coordinate. By making measurements of the signal at many discrete positions of the moving mirror, the spectrum can be reconstructed using a Fourier transform of the temporal coherence of the light. Michelson

The Fourier transform spectrometer is just a Michelson interferometer but one of the two fully-reflecting mirrors is movable, allowing a variable delay (in the travel-time of the light) to be included in one of the beams.
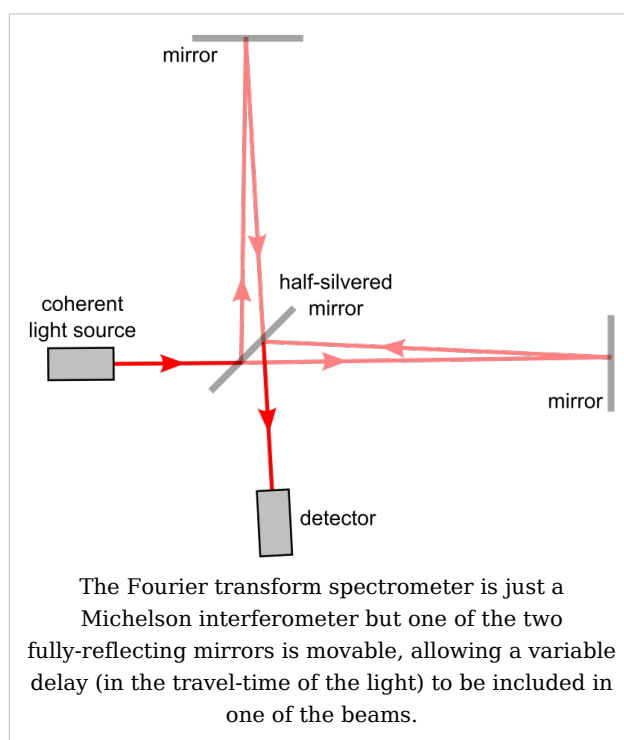
spectrographs are capable of very high spectral resolution observations of very bright sources. The Michelson or Fourier transform spectrograph was popular for infra-red applications at a time when infra-red astronomy only had single pixel detectors. Imaging Michelson spectrometers are a possibility, but in general have been supplanted by imaging Fabry-Perot instruments which are easier to construct.

Pulsed *Fourier transform* spectrometer

A pulsed *Fourier transform* spectrometer does not employ transmittance techniques. In the most general description of pulsed FT spectrometry, a sample is exposed to an energizing event which causes a periodic response. The frequency of the periodic response, as governed by the field conditions in the spectrometer, is indicative of the measured properties of the analyte.

Examples of Pulsed Fourier transform spectrometry

In magnetic spectroscopy (EPR, NMR), an RF pulse in a strong ambient magnetic field is used as the energizing event. This turns the magnetic particles at an angle to the ambient field, resulting in gyration. The gyrating spins then induce a periodic current in a detector coil. Each spin exhibits a characteristic frequency of gyration (relative to the field strength) which reveals information about the analyte.

In FT-mass spectrometry, the energizing event is the injection of the charged sample into the strong electromagnetic field of a cyclotron. These particles travel in circles, inducing a current in a fixed coil on one point in their circle. Each traveling particle exhibits a characteristic cyclotron frequency-field ratio revealing the masses in the sample.

The Free Induction Decay

Pulsed FT spectrometry gives the advantage of requiring a single, time-dependent measurement which can easily deconvolute a set of similar but distinct signals. The resulting composite signal, is called a *free induction decay,* because typically the signal will decay due to inhomogeneities in sample frequency, or simply unrecoverable loss of signal due to entropic loss of the property being measured.

Fellgett Advantage

One of the most important advantages of Fourier transform spectroscopy was shown by P.B. Fellgett, an early advocate of the method. The Fellgett advantage, also known as the multiplex principle, states that a multiplex spectrometer such as the Fourier transform spectroscopy will produce a gain of the order of the square root of m in the signal-to-noise ratio of the resulting spectrum, when compared with an equivalent scanning monochromator, where m is the number of elements comprising the resulting spectrum when the measurement noise is dominated by detector noise.

Converting spectra from time domain to frequency domain

$$S(t) = \int_{-\infty}^{\infty} I(\nu) e^{-i\nu 2\pi t} \, d\nu$$

The sum is performed over all contributing frequencies to give a signal S(t) in the time domain.

$$I(\nu) = 2Re \int_{-\infty}^{\infty} S(t) e^{2i\pi\nu t} dt$$

gives non-zero value when S(t) contains a component that matches the oscillating function. Remember that

$$e^{ix} = \cos x + i \sin x$$

See also

- Applied spectroscopy
- 2D-FT NMRI and Spectroscopy
- Forensic chemistry
- Forensic polymer engineering
- nuclear magnetic resonance
- Infra-red spectroscopy

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Further reading

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External links

- Description of how a Fourier transform spectrometer works (http://scienceworld. wolfram.com/physics/FourierTransformSpectrometer.html)
- The Michelson or Fourier transform spectrograph (http://www.astro.livjm.ac.uk/ courses/phys362/notes/)
- Internet Journal of Vibrational Spectroscopy - How FTIR works (http://www.ijvs.com/ volume5/edition5/section1.html#Feature)
- Fourier Transform Spectroscopy Topical Meeting and Tabletop Exhibit (http://www.osa. org/meetings/topicalmeetings/fts/default.aspx)

Nuclear Magnetic resonance imaging

Magnetic Resonance Imaging (**MRI**), or **nuclear magnetic resonance imaging** (**NMRI**), is primarily a medical imaging technique most commonly used in radiology to visualize the internal structure and function of the body. MRI provides much greater contrast between the different soft tissues of the body than computed tomography (CT) does, making it especially useful in neurological (brain), musculoskeletal, cardiovascular, and oncological (cancer) imaging. Unlike CT, it uses no ionizing radiation, but uses a powerful magnetic field to align the nuclear magnetization of (usually) hydrogen atoms in water in the body. Radio frequency (RF) fields are used to systematically alter the alignment of this magnetization, causing the hydrogen nuclei to produce

Para-sagittal MRI of the head, with aliasing artifacts (nose and forehead in the back of the head)

a rotating magnetic field detectable by the scanner. This signal can be manipulated by additional magnetic fields to build up enough information to construct an image of the body.[1] :36

Magnetic Resonance Imaging is a relatively new technology. The first MR image was published in 1973[2] and the first study performed on a human took place on July 3, 1977.[3][4] By comparison, the first human X-ray image was taken in 1895.

Magnetic Resonance Imaging was developed from knowledge gained in the study of nuclear magnetic resonance. In its early years the technique was referred to as nuclear magnetic resonance imaging (NMRI). However, as the word *nuclear* was associated in the public mind with ionizing radiation exposure it is generally now referred to simply as MRI. Scientists still use the term NMRI when discussing non-medical devices operating on the same principles. The term Magnetic Resonance Tomography (MRT) is also sometimes used.

How MRI works

The body is mainly composed of water molecules which each contain two hydrogen nuclei or protons. When a person goes inside the powerful magnetic field of the scanner, these protons align with the direction of the field.

A radio frequency electromagnetic field is then briefly turned on causing the protons to absorb some of its energy. When this field is turned off the protons release this energy at a resonance radio frequency which can be detected by the scanner. The frequency of the emitted signal depends on the strength of the magnetic field. The position of protons in the body can be determined by applying additional magnetic fields during the scan which allows an image of the body to be built up. These are created by turning gradients coils on and off which creates the knocking sounds heard during an MR scan.

Diseased tissue, such as tumors, can be detected because the protons in different tissues return to their equilibrium state at different rates. By changing the parameters on the scanner this effect is used to create contrast between different types of body tissue.

Contrast agents may be injected intravenously to enhance the appearance of blood vessels, tumors or inflammation. Contrast agents may also be directly injected into a joint in the case of arthrograms, MR images of joints. Unlike CT, scanning MRI uses no ionizing radiation and is generally a very safe procedure. Patients with some metal implants, cochlear implants, and cardiac pacemakers are prevented from having an MRI scan due to effects of the strong magnetic field and powerful radio frequency pulses.

MRI is used to image every part of the body, and is particularly useful for neurological conditions, for disorders of the muscles and joints, for evaluating tumors, and for showing abnormalities in the heart and blood vessels.

Physics principles

Nuclear magnetism

Subatomic particles such as protons have the quantum mechanical property of spin. Certain nuclei such as ^{1}H (protons), ^{2}H, ^{3}He, ^{23}Na or ^{31}P, have a non–zero spin and therefore a magnetic moment. In the case of the so-called spin-1/2 nuclei, such as ^{1}H, there are two spin states, sometimes referred to as "up" and "down". Nuclei such as ^{12}C have no unpaired neutrons or protons, and no net spin; however, the isotope ^{13}C (referred to as "carbon 13") does.

Modern 3 tesla clinical MRI scanner.

When these spins are placed in a strong external magnetic field they precess around an axis along the direction of the field. Protons align in two energy "eigenstates" (the "Zeeman effect"): one low-energy and one high-energy, which are separated by a certain splitting energy.

Resonance and relaxation

In the static magnetic fields commonly used in MRI, the energy difference between the nuclear spin states corresponds to a photon at radio frequency wavelengths. Resonant absorption of energy by the protons due to an external oscillating magnetic field will occur at the Larmor frequency for the particular nucleus.

The net magnetization vector has two components. The longitudinal magnetization is due to a tiny excess of protons in the lower energy state. This gives a net polarization parallel to the external field. Application of an RF pulse can destroy (with a so-called 90° pulse) or even reverse (with a so-called 180° pulse) this polarization vector. The transverse magnetization is due to coherences forming between the two proton energy states following an RF pulse typically of 90°. This gives a net polarization perpendicular to the external field

in the transverse plane. The recovery of longitudinal magnetization is called longitudinal or T_1 relaxation and occurs exponentially with a time constant T_1. The loss of phase coherence in the transverse plane is called transverse or T_2 relaxation. T_1 is thus associated with the enthalpy of the spin system (the number of nuclei with parallel versus anti-parallel spin) while T_2 is associated with its entropy (the number of nuclei in phase).

When the radio frequency pulse is turned off, the transverse vector component produces an oscillating magnetic field which induces a small current in the receiver coil. This signal is called the free induction decay (FID). In an idealized nuclear magnetic resonance experiment, the FID decays approximately exponentially with a time constant T_2, but in practical MRI small differences in the static magnetic field at different spatial locations ("inhomogeneities") cause the Larmor frequency to vary across the body creating destructive interference which shortens the FID. The time constant for the observed decay of the FID is called the T_2* ("T 2 star") relaxation time, and is always shorter than T_2. Also, when the radio frequency pulse is turned off, the longitudinal magnetization starts to recover exponentially with a time constant T_1.

In MRI, the static magnetic field is caused to vary across the body (a field gradient), so that different spatial locations become associated with different precession frequencies. Usually these field gradients are pulsed, and it is the almost infinite variety of RF and gradient pulse sequences that gives MRI its versatility. Application of field gradient destroys the FID signal, but this can be recovered and measured by a refocusing gradient (to create a so-called "gradient echo"), or by a radio frequency pulse (to create a so-called "spin-echo"). The whole process can be repeated when some T_1-relaxation has occurred and the thermal equilibrium of the spins has been more or less restored.

Typically in soft tissues T_1 is around one second while T_2 and T_2* are a few tens of milliseconds, but these values vary widely between different tissues (and different external magnetic fields), giving MRI its tremendous soft tissue contrast.

Contrast agents work by altering (shortening) the relaxation parameters, especially T_1.

Imaging

A number of schemes have been devised for combining field gradients and radio frequency excitation to create an image:

- 2D or 3D reconstruction from projections, much as in Computed Tomography.
- Building the image point-by-point or line-by-line.
- Gradients in the RF field rather than the static field.

Although each of these schemes is occasionally used in specialist applications, the majority of MR Images today are created either by the Two-Dimensional Fourier Transform (2DFT) technique with slice selection, or by the Three-Dimensional Fourier Transform (3DFT) technique. Another name for 2DFT is spin-warp. What follows here is a description of the 2DFT technique with slice selection.

The 3DFT technique is rather similar except that there is no slice selection and phase-encoding is performed in two separate directions.

Another scheme which is sometimes used, especially in brain scanning or where images are needed very rapidly, is called echo-planar imaging (EPI): In this case, each RF excitation is followed by a train of gradient echoes with different spatial encoding.

Image contrast and contrast enhancement

Image contrast is created by differences in the strength of the NMR signal recovered from different locations within the sample. This depends upon the relative density of excited nuclei (usually water protons), on differences in relaxation times (T_1, T_2 and T_2*) of those nuclei after the pulse sequence, and often on other parameters discussed under specialized MR scans. Contrast in most MR images is actually a mixture of all these effects, but careful design of the imaging pulse sequence allows one contrast mechanism to be emphasized while the others are minimized. The ability to choose different contrast mechanisms gives MRI tremendous flexibility. In the brain, T_1-weighting causes the nerve connections of white matter to appear white, and the congregations of neurons of gray matter to appear gray, while cerebrospinal fluid (CSF) appears dark. The contrast of white matter, gray matter and cerebrospinal fluid is reversed using T_2 or T_2* imaging, whereas proton-density-weighted imaging provides little contrast in healthy subjects. Additionally, functional parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV) or blood oxygenation can affect T_1, T_2 and T_2* and so can be encoded with suitable pulse sequences.

In some situations it is not possible to generate enough image contrast to adequately show the anatomy or pathology of interest by adjusting the imaging parameters alone, in which case a contrast agent may be administered. This can be as simple as water, taken orally, for imaging the stomach and small bowel. However, most contrast agents used in MRI are selected for their specific magnetic properties. Most commonly, a paramagnetic contrast agent (usually a gadolinium compound[5] [6]) is given. Gadolinium-enhanced tissues and fluids appear extremely bright on T_1-weighted images. This provides high sensitivity for detection of vascular tissues (*e.g.*, tumors) and permits assessment of brain perfusion (*e.g.*, in stroke). There have been concerns raised recently regarding the toxicity of gadolinium-based contrast agents and their impact on persons with impaired kidney function. The American College of Radiology released screening criteria for patients intended to be given gadolinium-based contrast agents [7] to identify potential risk factors for negative reactions. Special actions may be taken, such as hemodialysis following a contrast MRI scan for renally-impaired patients.

More recently, superparamagnetic contrast agents, *e.g.*, iron oxide nanoparticles[8] [9] , have become available. These agents appear very dark on T_2*-weighted images and may be used for liver imaging, as normal liver tissue retains the agent, but abnormal areas (*e.g.*, scars, tumors) do not. They can also be taken orally, to improve visualization of the gastrointestinal tract, and to prevent water in the gastrointestinal tract from obscuring other organs (*e.g.*, the pancreas). Diamagnetic agents such as barium sulfate have also been studied for potential use in the gastrointestinal tract, but are less frequently used.

K-space

In 1983 Ljunggren[10] and Tweig[11] independently introduced the k-space formalism, a technique that proved invaluable in unifying different MR imaging techniques. They showed that the demodulated MR signal $S(t)$ generated by freely precessing nuclear spins in the presence of a linear magnetic field gradient G equals the Fourier transform of the effective spin density, *i.e.*

$$S(t) = \tilde{\rho}_{\text{eff}}(\vec{k}(t)) \equiv \int \mathrm{d}\vec{x}\ \rho(\vec{x}) \cdot e^{2\pi\imath\ \vec{k}(t)\cdot\vec{x}}$$

where:

$$\vec{k}(t) \equiv \int_0^t \vec{G}(\tau) \, \mathrm{d}\tau$$

In other words, as time progresses the signal traces out a trajectory in k-space with the velocity vector of the trajectory proportional to the vector of the applied magnetic field gradient. By the term *effective spin density* we mean the true spin density $\rho(\vec{x})$ corrected for the effects of T_1 preparation, T_2 decay, dephasing due to field inhomogeneity, flow, diffusion, *etc.* and any other phenomena that affect that amount of transverse magnetization available to induce signal in the RF probe.

From the basic k-space formula, it follows immediately that we reconstruct an image $I(\vec{x})$ simply by taking the inverse Fourier transform of the sampled data, *viz.*

$$I(\vec{x}) = \int \mathrm{d}\vec{k} \; S(\vec{k}(t)) \cdot e^{-2\pi \imath \; \vec{k}(t) \cdot \vec{x}}$$

Using the k-space formalism, a number of seemingly complex ideas became simple. For example, it becomes very easy to understand the role of phase encoding (the so-called spin-warp method). In a standard spin echo or gradient echo scan, where the readout (or view) gradient is constant (*e.g.* G_x), a single line of k-space is scanned per RF excitation. When the phase encoding gradient is zero, the line scanned is the k_x axis. When a non-zero phase-encoding pulse is added in between the RF excitation and the commencement of the readout gradient, this line moves up or down in k-space, *i.e.*, we scan the line k_y =constant.

The k-space formalism also makes it very easy to compare different scanning techniques. In single-shot EPI, all of k-space is scanned in a single shot, following either a sinusoidal or zig-zag trajectory. Since alternating lines of k-space are scanned in opposite directions, this must be taken into account in the reconstruction. Multi-shot EPI and fast spin echo techniques acquire only part of k-space per excitation. In each shot, a different interleaved segment is acquired, and the shots are repeated until k-space is sufficiently well-covered. Since the data at the center of k-space represent lower spatial frequencies than the data at the edges of k-space, the T_E value for the center of k-space determines the image's T_2 contrast.

The importance of the center of k-space in determining image contrast can be exploited in more advanced imaging techniques. One such technique is spiral acquisition - a rotating magnetic field gradient is applied, causing the trajectory in k-space to spiral out from the center to the edge. Due to T_2 and T_2* decay the signal is greatest at the start of the acquisition, hence acquiring the center of k-space first improves contrast to noise ratio (CNR) when compared to conventional zig-zag acquisitions, especially in the presence of rapid movement.

Since $\vec{x}$ and $\vec{k}$ are conjugate variables (with respect to the Fourier transform) we can use the Nyquist theorem to show that the step in k-space determines the field of view of the image (maximum frequency that is correctly sampled) and the maximum value of k sampled determines the resolution, *i.e.*

$$FOV \propto \frac{1}{\Delta k} \qquad \text{Resolution} \propto |k_{\mathrm{max}}|$$

(these relationships apply to each axis [X, Y, and Z] independently).

Example of a pulse sequence

Simplified timing diagram for two-dimensional-Fourier-transform (2DFT) Spin Echo (SE) pulse sequence
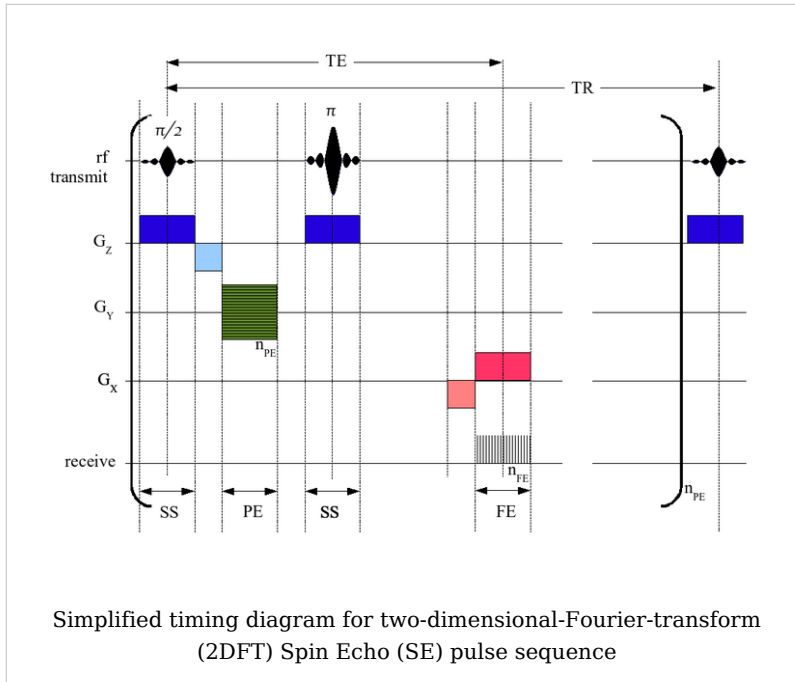
In the timing diagram, the horizontal axis represents time. The vertical axis represents: (top row) amplitude of radio frequency pulses; (middle rows) amplitudes of the three orthogonal magnetic field gradient pulses; and (bottom row) receiver analog-to-digital converter (ADC). Radio frequencies are transmitted at the Larmor frequency of the nuclide to be imaged. For example, for ^{1}H in a magnetic field of 1T, a frequency of 42.5781 MHz would be employed. The three field gradients are labeled G_X (typically corresponding to a patient's Left-to-Right direction and colored red in diagram), G_Y (typically corresponding to a patient's Front-to-Back direction and colored green in diagram), and G_Z (typically corresponding to a patient's Head-to-Toe direction and colored blue in diagram). Where negative-going gradient pulses are shown, they represent reversal of the gradient direction, *i.e.*, Right-to-Left, Back-to-Front or Toe-to-Head. For human scanning, gradient strengths of 1-100 mT/m are employed: Higher gradient strengths permit better resolution and faster imaging. The pulse sequence shown here would produce a transverse (axial) image.

The first part of the pulse sequence, SS, achieves Slice Selection. A shaped pulse (shown here with a sinc modulation) causes a 90° (π/2 radian) nutation of longitudinal nuclear magnetization within a slab, or slice, creating transverse magnetization. The second part of the pulse sequence, PE, imparts a phase shift upon the slice-selected nuclear magnetization, varying with its location in the Y direction. The third part of the pulse sequence, another Slice Selection (of the same slice) uses another shaped pulse to cause a 180° (π radian) rotation of transverse nuclear magnetization within the slice. This transverse magnetisation refocuses to form a spin echo at a time TE. During the spin echo, a frequency-encoding (FE) or readout gradient is applied, making the resonant frequency of the nuclear magnetization vary with its location in the X direction. The signal is sampled n_{FE} times by the ADC during this period, as represented by the vertical lines. Typically n_{FE} of between 128 and 512 samples are taken.

The longitudinal relaxation is then allowed to recover somewhat and after a time TR the whole sequence is repeated n_{PE} times, but with the phase-encoding gradient incremented (indicated by the horizontal hatching in the green gradient block). Typically n_{PE} of between 128 and 512 repetitions are made.

The negative-going lobes in G_X and G_Z are imposed to ensure that, at time TE (the spin echo maximum), phase only encodes spatial location in the Y direction.

Typically TE is between 5 ms and 100 ms, while TR is between 100 ms and 2000 ms.

After the two-dimensional matrix (typical dimension between 128x128 and 512x512) has been acquired, producing the so-called K-space data, a two-dimensional Fourier transform is performed to provide the familiar MR image. Either the magnitude or phase of the Fourier transform can be taken, the former being far more common.

Scanner construction and operation

The major components of an MRI scanner are: the main magnet, which polarizes the sample, the shim coils for correcting inhomogeneities in the main magnetic field, the gradient system which is used to localize the MR signal and the RF system, which excites the sample and detects the resulting NMR signal. The whole system is controlled by one or more computers.

Magnet

The magnet is the largest and most expensive component of the scanner, and the remainder of the scanner is built around it. The strength of the magnet is measured in tesla (T). Clinical magnets generally have a field strength in the range 0.1—3.0 T, with research systems available up to 9.4 T for human use and 21 T for animal systems[12] .

Just as important as the strength of the main magnet is its precision. The straightness of the magnetic lines within the center (or, as it is technically known, the iso-center) of the magnet needs to be near-perfect. This is known as homogeneity. Fluctuations (inhomogeneities in the field strength) within the scan region should be less than three parts per million (3 ppm). Three types of magnets have been used:

Schematic of construction of a cylindrical superconducting MR scanner

- Permanent magnet: Conventional magnets made from ferromagnetic materials (*e.g.*, steel alloys containing rare earth elements such as neodymium) can be used to provide the static magnetic field. A permanent magnet that is powerful enough to be used in an MRI will be extremely large and bulky; they can weigh over 100 tonnes. Permanent magnet MRIs are very inexpensive to maintain; this cannot be said of the other types of MRI magnets, but there are significant drawbacks to using permanent magnets. They are only capable of achieving weak field strengths compared to other MRI magnets (usually less than 0.4 T) and they are of limited precision and stability. Permanent magnets also present special safety issues; since their magnetic fields cannot be "turned off," ferromagnetic objects are virtually impossible to remove from them once they come into direct contact. Permanent magnets also require special care when they are being brought to their site of installation.
- Resistive electromagnet: A solenoid wound from copper wire is an alternative to a permanent magnet. An advantage is low initial cost, but field strength and stability are limited. The electromagnet requires considerable electrical energy during operation which can make it expensive to operate. This design is essentially obsolete.
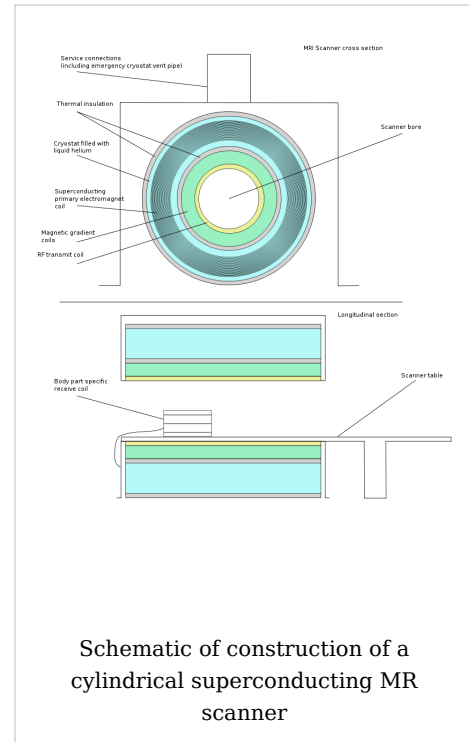
- Superconducting electromagnet: When a niobium-titanium or niobium-tin alloy is cooled by liquid helium to 4K (−269°C, −452°F) it becomes a superconductor, losing resistance to flow of electrical current. An electromagnet constructed with superconductors can have extremely high field strengths, with very high stability. The construction of such magnets is extremely costly, and the cryogenic helium is expensive and difficult to handle. However, despite their cost, helium cooled superconducting magnets are the most common type found in MRI scanners today.

Most superconducting magnets have their coils of superconductive wire immersed in liquid helium, inside a vessel called a cryostat. Despite thermal insulation, ambient heat causes the helium to slowly boil off. Such magnets, therefore, require regular topping-up with liquid helium. Generally a cryocooler, also known as a coldhead, is used to recondense some helium vapor back into the liquid helium bath. Several manufacturers now offer 'cryogenless' scanners, where instead of being immersed in liquid helium the magnet wire is cooled directly by a cryocooler.

Magnets are available in a variety of shapes. However, permanent magnets are most frequently 'C' shaped, and superconducting magnets most frequently cylindrical. However, C-shaped superconducting magnets and box-shaped permanent magnets have also been used.

Magnetic field strength is an important factor in determining image quality. Higher magnetic fields increase signal-to-noise ratio, permitting higher resolution or faster scanning. However, higher field strengths require more costly magnets with higher maintenance costs, and have increased safety concerns. A field strength of 1.0 - 1.5 T is a good compromise between cost and performance for general medical use. However, for certain specialist uses (*e.g.*, brain imaging) higher field strengths are desirable, with some hospitals now using 3.0 T scanners.

Shims

When a sample is placed into the scanner, the main magnetic field is distorted by susceptibility boundaries within that sample, causing signal dropout (regions showing no signal) and spatial distortions in acquired images. For humans or animals the effect is particularly pronounced at air-tissue boundaries such as the sinuses (due to paramagnetic oxygen in air) making, for example, the frontal lobes of the brain difficult image. To restore field homogeneity a set of shim coils are included in the scanner. These are resistive coils,

FID signal from a badly shimmed sample has a complex envelope.

usually at room temperature, capable of producing field corrections distributed as several orders of spherical harmonics.[13]

After placing the sample in the scanner, the B0 field is 'shimmed' by adjusting currents in the shim coils. Field homogeneity is measured by examining an FID signal in the absence of field gradients. The FID from a poorly
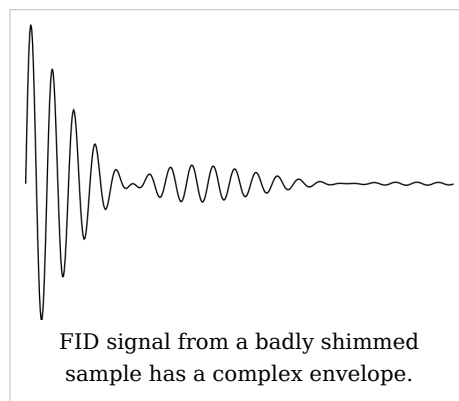
shimmed sample will show a complex decay envelope, often with many humps. Shim currents are then adjusted to produce a large amplitude exponentially decaying FID, indicating a homogeneous B0 field. The process is usually automated.[14]

FID signal from a well shimmed sample, showing a pure exponential decay.
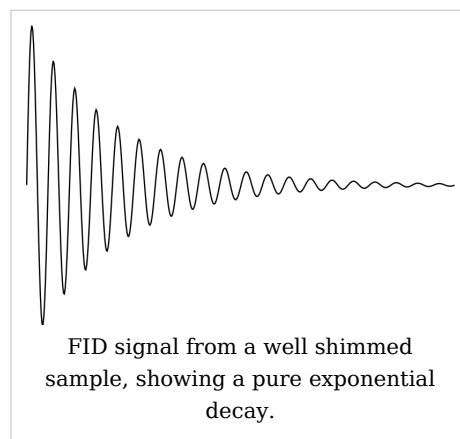
Gradients

Gradient coils are used to spatially encode the positions of protons by varying the magnetic field linearly across the imaging volume. The Larmor frequency will then vary as a function of position in the x, y and z-axes.

Gradient coils are usually resistive electromagnets powered by sophisticated amplifiers which permit rapid and precise adjustments to their field strength and direction. Typical gradient systems are capable of producing gradients from 20 mT/m to 100 mT/m (*i.e.*, in a 1.5 T magnet, when a maximal z-axis gradient is applied, the field strength may be 1.45 T at one end of a 1 m long bore and 1.55 T at the other[15]). It is the magnetic gradients that determine the plane of imaging - because the orthogonal gradients can be combined freely, any plane can be selected for imaging.

Scan speed is dependent on performance of the gradient system. Stronger gradients allow for faster imaging, or for higher resolution; similarly, gradients systems capable of faster switching can also permit faster scanning. However, gradient performance is limited by safety concerns over nerve stimulation.

Some important characteristic of gradient amplifiers and gradient coil are slew rate and gradient strength. As mentioned earlier, a gradient coil will create an additional, linearly varying magnetic field that adds or subtracts from the main magnetic field. This additional magnetic field will have components in all 3 directions, *viz.* X, Y and Z; however, only the component along the magnetic field (usually called the Z-axis, hence denoted G_z) is useful for imaging. Along any given axis, the gradient will add to the magnetic field on one side of the zero position and subtract from it on the other side. Since the additional field is a gradient, it has units of gauss per cm or millitesla (mT) per meter. High performance gradient coils used in MRI are typically capable of producing a gradient magnetic field of approximate 30 mT per meter or higher for a 1.5 T MRI. The slew rate of a gradient system is a measure of how quickly the gradients can be ramped on or off. Typical higher performance gradients have a slew rate of up to 100-200 tesla per meter per second. The slew rate depends both on the gradient coil (it takes more time to ramp up or down a large coil than a small coil) and on the performance of the gradient amplifier (it takes a lot of voltage to overcome the inductance of the coil) and has adequate influence on image quality.

Radio frequency system

The radio frequency (RF) transmission system consists of an RF synthesizer, power amplifier and transmitting coil. This is usually built into the body of the scanner. The power of the transmitter is variable, but high-end scanners may have a peak output power of up to 35 kW, and be capable of sustaining average power of 1 kW. The receiver consists of the coil, pre-amplifier and signal processing system. While it is possible to scan using the integrated coil for RF transmission and MR signal reception, if a small region is being imaged, then better image quality (*i.e.*, signal-to-noise ratio) is obtained by using a close-fitting smaller coil. A variety of coils are available which fit closely around parts of the body, *e.g.*, the head, knee, wrist, breast, or internally, *e.g.*, the rectum.

A recent development in MRI technology has been the development of sophisticated multi-element phased array[16] coils which are capable of acquiring multiple channels of data in parallel. This 'parallel imaging' technique uses unique acquisition schemes that allow for accelerated imaging, by replacing some of the spatial coding originating from the magnetic gradients with the spatial sensitivity of the different coil elements. However, the increased acceleration also reduces the signal-to-noise ratio and can create residual artifacts in the image reconstruction. Two frequently used parallel acquisition and reconstruction schemes are known as SENSE[17] and GRAPPA.[18] A detailed review of parallel imaging techniques can be found here:[19]

Applications

In clinical practice, MRI is used to distinguish pathologic tissue (such as a brain tumor) from normal tissue. One advantage of an MRI scan is that it is harmless to the patient. It uses strong magnetic fields and non-ionizing radiation in the radio frequency range. Compare this to CT scans and traditional X-rays which involve doses of ionizing radiation and may increase the risk of malignancy, especially in a fetus.

While CT provides good spatial resolution (the ability to distinguish two structures an arbitrarily small distance from each other as separate), MRI provides comparable resolution with far better contrast resolution (the ability to distinguish the differences between two arbitrarily similar but not identical tissues). The basis of this ability is the complex library of *pulse sequences* that the modern medical MRI scanner includes, each of which is optimized to provide *image contrast* based on the chemical sensitivity of MRI.

For example, with particular values of the *echo time* (TE) and the *repetition time* (TR), which are basic parameters of image acquisition, a sequence will take on the property of T_2-weighting. On a T_2-weighted scan, water- and fluid-containing tissues are bright (most modern T_2 sequences are actually *fast* T_2 sequences) and fat-containing tissues are dark. The reverse is true for T_1-weighted images. Damaged tissue tends to develop edema, which makes a T_2-weighted sequence sensitive for pathology, and generally able to distinguish pathologic tissue from normal tissue. With the addition of an additional radio frequency pulse and additional manipulation of the magnetic gradients, a T_2-weighted sequence can be converted to a **FLAIR** sequence, in which free water is now dark, but edematous tissues remain bright. This sequence in particular is currently the most sensitive way to evaluate the brain for demyelinating diseases, such as multiple sclerosis.

The typical MRI examination consists of 5-20 sequences, each of which are chosen to provide a particular type of information about the subject tissues. This information is then synthesized by the interpreting physician.

Basic MRI scans

Comparison of Different Types of MR Contrast

| T_2 weighting | FLAIR | T_2* weighting | T_1 weighting with gadolinium contrast |
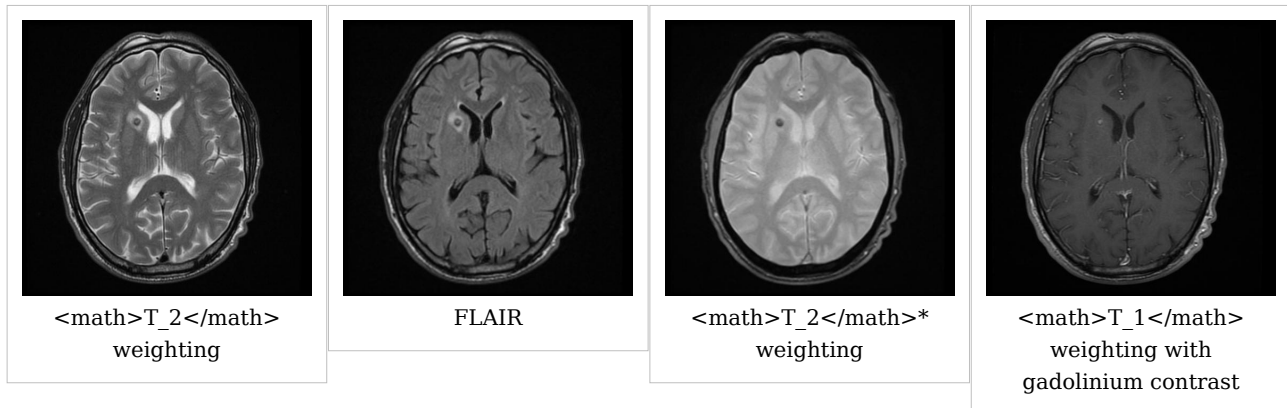
T_1-weighted MRI

T_1-weighted scans use a gradient echo (GRE) sequence, with short TE and short TR. This is one of the basic types of MR contrast and is a commonly run clinical scan. The T_1 weighting can be increased (improving contrast) with the use of an inversion pulse as in an MP-RAGE sequence. Due to the short repetition time (TR) this scan can be run very fast allowing the collection of high resolution 3D datasets. A T_1 reducing gadolinium contrast agent is also commonly used, with a T_1 scan being collected before and after administration of contrast agent to compare the difference. In the brain T_1-weighted scans provide good gray matter/white matter contrast.

T_2-weighted MRI

T_2-weighted scans use a spin echo (SE) sequence, with long TE and long TR. They have long been the clinical workhorse as the spin echo sequence is less susceptible to inhomogeneities in the magnetic field. They are particularly well suited to edema as they are sensitive to water content (edema is characterized by increased water content).

T_2*-weighted MRI

T_2* (pronounced "T 2 star") weighted scans use a gradient echo (GRE) sequence, with long TE and long TR. The gradient echo sequence used does not have the extra refocusing pulse used in spin echo so it is subject to additional losses above the normal T_2 decay (referred to as T_2'), these taken together are called T_2*. This also makes it more prone to susceptibility losses at air/tissue boundaries, but can increase contrast for certain types of tissue, such as venous blood.

Spin density weighted MRI

Spin density, also called proton density, weighted scans try to have no contrast from either T_2 or T_1 decay, the only signal change coming from differences in the amount of available spins. It uses a spin echo or sometimes a gradient echo sequence, with short TE and long TR.

Specialized MRI scans

Diffusion MRI

Diffusion MRI measures the diffusion of water molecules in biological tissues.[20] In an isotropic medium (inside a glass of water for example) water molecules naturally move randomly according to Brownian motion. In biological tissues however, the diffusion may be anisotropic. For example a molecule inside the axon of a neuron has a low probability of crossing the myelin membrane. Therefore the molecule will move principally along the axis of the neural fiber. If we know that molecules in a particular voxel diffuse principally in one direction we can make the assumption that the majority of the fibers in this area are going parallel to that direction.
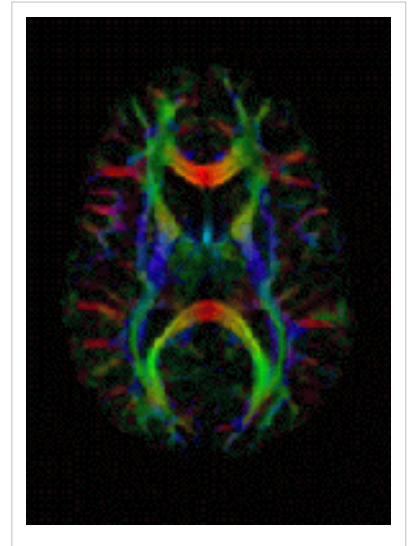
The recent development of diffusion tensor imaging (DTI) enables diffusion to be measured in multiple directions and the fractional anisotropy in each direction to be calculated for each voxel. This enables researchers to make brain maps of fiber directions to examine the connectivity of different regions in the brain (using tractography) or to examine areas of neural degeneration and demyelination in diseases like Multiple Sclerosis.

Another application of diffusion MRI is diffusion-weighted imaging (DWI). Following an ischemic stroke, DWI is highly sensitive to the changes occurring in the lesion.[21] It is speculated that increases in restriction (barriers) to water diffusion, as a result of cytotoxic edema (cellular swelling), is responsible for the increase in signal on a DWI scan. The DWI enhancement appears within 5–10 minutes of the onset of stroke symptoms (as compared with computed tomography, which often does not detect changes of acute infarct for up to 4–6 hours) and remains for up to two weeks. Coupled with imaging of cerebral perfusion, researchers can highlight regions of "perfusion/diffusion mismatch" that may indicate regions capable of salvage by reperfusion therapy.

Like many other specialized applications, this technique is usually coupled with a fast image acquisition sequence, such as echo planar imaging sequence.

Magnetization Transfer MRI

Magnetization transfer (MT) refers to the transfer of longitudinal magnetization from free water protons to hydration water protons in NMR and MRI.

In magnetic resonance imaging of molecular solutions, such as protein solutions, two types of water molecules, free (bulk) and hydration, are found. Free water protons have faster average rotational frequency and hence less fixed water molecules that may cause local field inhomogeneity. Because of this uniformity, most free water protons have resonance frequency lying narrowly around the normal proton resonance frequency of 63 MHz (at 1.5 tesla). This also results in slower transverse magnetization dephasing and hence longer T_2. Conversely, hydration water molecules are slowed down by interaction with solute molecules and hence create field inhomogeneities that lead to wider resonance frequency spectrum.

Fluid attenuated inversion recovery (FLAIR)

Fluid Attenuated Inversion Recovery (FLAIR)[22] , is an inversion-recovery pulse sequence used to null signal from fluids. For example, it can be used in brain imaging to suppress Cerebrospinal fluid (CSF) so as to bring out the periventricular hyperintense lesions, such as multiple sclerosis (MS) plaques. By carefully choosing the inversion time TI (the time between the inversion and excitation pulses), signal from any particular tissue can be suppressed.

Magnetic resonance angiography

Magnetic resonance angiography (MRA) is used to generate pictures of the arteries in order to evaluate them for stenosis (abnormal narrowing) or aneurysms (vessel wall dilatations, at risk of rupture). MRA is often used to evaluate the arteries of the neck and brain, the thoracic and abdominal aorta, the renal arteries, and the legs (called a "run-off"). A variety of techniques can be used to generate the pictures, such as administration of a paramagnetic contrast agent (gadolinium) or using a technique known as "flow-related enhancement" (e.g. 2D and 3D time-of-flight sequences), where most of the signal on an image is due to blood which has recently moved into that plane, see also FLASH MRI. Techniques involving phase accumulation

Magnetic Resonance Angiography

(known as phase contrast angiography) can also be used to generate flow velocity maps easily and accurately. Magnetic resonance venography (MRV) is a similar procedure that is used to image veins. In this method the tissue is now excited inferiorly while signal is gathered in the plane immediately superior to the excitation plane, and thus imaging the venous blood which has recently moved from the excited plane.

Magnetic Resonance Gated Intracranial CSF Dynamics (MR-GILD)

Magnetic resonance gated intracranial cerebrospinal fluid (CSF)or liquor dynamics (MR-GILD) technique is an MR sequence based on bipolar gradient pulse used to demonstrate CSF pulsatile flow in ventricles, cisterns, aqueduct of Sylvius and entire intracranial CSF pathway. It is a method for analyzing CSF circulatory system dynamics in patients with CSF obstructive lesions such as normal pressure hydrocephalus. It also allows visualization of both arterial and venous pulsatile blood flow in vessels without use of contrast agents. [23] [24] .

Diastolic time data acquisition (DTDA).	Systolic time data acquisition (STDA).
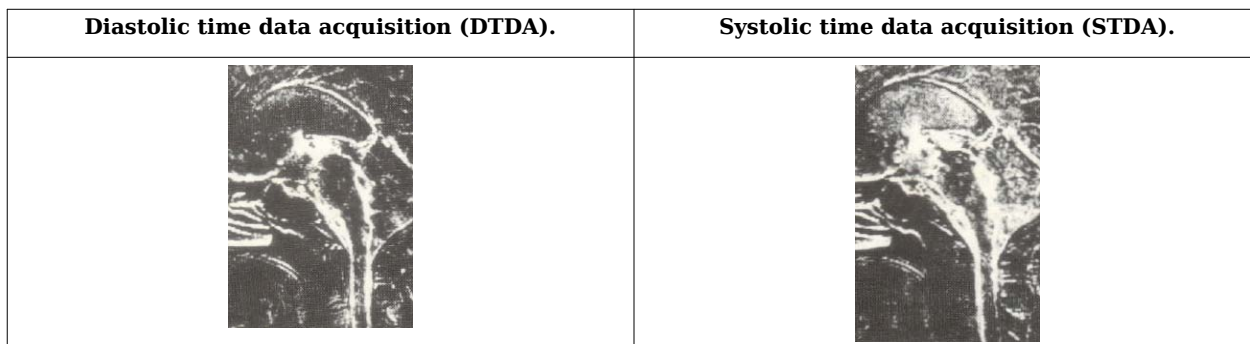
Magnetic resonance spectroscopy

Magnetic resonance spectroscopy is used to measure the levels of different metabolites in body tissues. The MR signal produces a spectrum of resonances that correspond to different molecular arrangements of the isotope being "excited". This signature is used to diagnose certain metabolic disorders, especially those affecting the brain,[25] as well as to provide information on tumor metabolism.[26]

Magnetic resonance spectroscopic imaging (MRSI) combines both spectroscopic and imaging methods to produce spatially localized spectra from within the sample or patient. The spatial resolution is much lower (limited by the available SNR), but the spectra in each voxel contains information about many metabolites. Because the available signal is used to encode spatial and spectral information, MRSI requires high SNR achievable only at higher field strengths (1.5T and above).

Functional MRI

Functional MRI (fMRI) measures signal changes in the brain that are due to changing neural activity. The brain is scanned at low resolution but at a rapid rate (typically once every 2–3 seconds). Increases in neural activity cause changes in the MR signal via T_2* changes;[27] this mechanism is referred to as the BOLD (blood-oxygen-level dependent) effect. Increased neural activity causes an increased demand for oxygen, and the vascular system actually overcompensates for this, increasing the amount of oxygenated hemoglobin relative to deoxygenated hemoglobin. Because deoxygenated hemoglobin attenuates the MR signal,
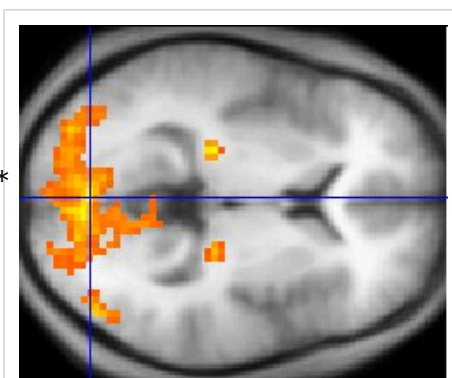
A fMRI scan showing regions of activation in orange, including the primary visual cortex (V1, BA17).

the vascular response leads to a signal increase that is related to the neural activity. The precise nature of the relationship between neural activity and the BOLD signal is a subject of current research. The BOLD effect also allows for the generation of high resolution 3D maps of the venous vasculature within neural tissue.

While BOLD signal is the most common method employed for neuroscience studies in human subjects, the flexible nature of MR imaging provides means to sensitize the signal to other aspects of the blood supply. Alternative techniques employ arterial spin labeling (ASL) or weight the MRI signal by cerebral blood flow (CBF) and cerebral blood volume (CBV). The CBV method requires injection of a class of MRI contrast agents that are now in human clinical trials. Because this method has been shown to be far more sensitive than the BOLD technique in preclinical studies, it may potentially expand the role of fMRI in clinical applications. The CBF method provides more quantitative information than the BOLD signal, albeit at a significant loss of detection sensitivity.

Interventional MRI

The lack of harmful effects on the patient and the operator make MRI well-suited for "interventional radiology", where the images produced by a MRI scanner are used to guide minimally-invasive procedures. Of course, such procedures must be done without *any* ferromagnetic instruments.

A specialized growing subset of interventional MRI is that of intraoperative MRI in which the MRI is used in the surgical process. Some specialized MRI systems have been developed that allow imaging concurrent with the surgical procedure. More typical, however, is that the surgical procedure is temporarily interrupted so that MR images can be acquired to verify the success of the procedure or guide subsequent surgical work.

Radiation therapy simulation

Because of MRI's superior imaging of soft tissues, it is now being utilized to specifically locate tumors within the body in preparation for radiation therapy treatments. For therapy simulation, a patient is placed in specific, reproducible, body position and scanned. The MRI system then computes the precise location, shape and orientation of the tumor mass, correcting for any spatial distortion inherent in the system. The patient is then marked or tattooed with points which, when combined with the specific body position, will permit precise triangulation for radiation therapy.

Current density imaging

Current density imaging (CDI) endeavors to use the phase information from images to reconstruct current densities within a subject. Current density imaging works because electrical currents generate magnetic fields, which in turn affect the phase of the magnetic dipoles during an imaging sequence. To date no successful CDI has been performed using biological currents, but several studies have been published which involve applied currents through a pair of electrodes.

Magnetic resonance guided focused ultrasound

In MRgFUS therapy, ultrasound beams are focused on a tissue - guided and controlled using MR thermal imaging - and due to the significant energy deposition at the focus, temperature within the tissue rises to more than 65°C, completely destroying it. This technology can achieve precise "ablation" of diseased tissue. MR imaging provides a three-dimensional view of the target tissue, allowing for precise focusing of ultrasound energy. The MR imaging provides quantitative, real-time, thermal images of the treated area. This allows the physician to ensure that the temperature generated during each cycle of ultrasound energy is sufficient to cause thermal ablation within the desired tissue and if not, to adapt the parameters to ensure effective treatment.

Multinuclear imaging

Hydrogen is the most frequently imaged nucleus in MRI because it is present in biological tissues in great abundance. However, any nucleus which has a net nuclear spin could potentially be imaged with MRI. Such nuclei include helium-3, carbon-13, fluorine-19, oxygen-17, sodium-23, phosphorus-31 and xenon-129. ^{23}Na and ^{31}P are naturally abundant in the body, so can be imaged directly. Gaseous isotopes such as ^{3}He or ^{129}Xe must be hyperpolarized and then inhaled as their nuclear density is too low to yield a useful signal under normal conditions. ^{17}O, ^{13}C and ^{19}F can be administered in sufficient quantities in liquid form (e.g. ^{17}O-water, ^{13}C-glucose solutions or perfluorocarbons) that hyperpolarization is not a necessity.

Multinuclear imaging is primarily a research technique at present. However, potential applications include functional imaging and imaging of organs poorly seen on ^{1}H MRI (e.g. lungs and bones) or as alternative contrast agents. Inhaled hyperpolarized ^{3}He can be used to image the distribution of air spaces within the lungs. Injectable solutions containing ^{13}C or stabilized bubbles of hyperpolarized ^{129}Xe have been studied as contrast agents for angiography and perfusion imaging. ^{31}P can potentially provide information on bone density and structure, as well as functional imaging of the brain.

Susceptibility weighted imaging (SWI)

Susceptibility weighted imaging (SWI), is a new type of contrast in MRI different from spin density, T_1, or T_2 imaging. This method exploits the susceptibility differences between tissues and uses a fully velocity compensated, three dimensional, RF spoiled, high-resolution, 3D gradient echo scan. This special data acquisition and image processing produces an enhanced contrast magnitude image very sensitive to venous blood, hemorrhage and iron storage. It is used to enhance the detection and diagnosis of tumors, vascular and neurovascular diseases (stroke and hemorrhage, multiple sclerosis, Alzheimer's), and also detects traumatic brain injuries that may not be diagnosed using other methods.[28]

Other specialized MRI techniques

MRI is a new and active field of research and new methods and variants are often published when they are able to get better results in specific fields. Examples of these recent improvements are T_2*-weighted turbo spin-echo (T_2TSE MRI), Double inversion recovery MRI (DIR-MRI) or Phase-sensitive inversion recovery MRI (PSIR-MRI), all of them able to improve imaging of the brain lesions[29] [30] . Another example is MP-RAGE (magnetization-prepared rapid acquisition with gradient echo)[31] , which improves images

of multiple sclerosis cortical lesions[32] .

Portable instruments

Portable magnetic resonance instruments are available for use in education and field research. Using the principles of Earth's field NMR, they have no powerful polarizing magnet, so that such instruments can be small and relatively inexpensive. Some can be used for both EFNMR spectroscopy and MRI imaging[33] . The low strength of the Earth's field results in poor signal to noise ratios, requiring relatively long scan times to capture spectroscopic data or build up MRI images.

Research with atomic magnetometers have discussed the possibility for cheap and portable MRI instruments without the large magnet.[34] [35]

MRI versus CT

A computed tomography (CT) scanner uses X-rays, a type of ionizing radiation, to acquire its images, making it a good tool for examining tissue composed of elements of a higher atomic number than the tissue surrounding them, such as bone and calcifications (calcium based) within the body (carbon based flesh), or of structures (vessels, bowel). MRI, on the other hand, uses non-ionizing radio frequency (RF) signals to acquire its images and is best suited for non-calcified tissue, though MR images can also be acquired from bones and teeth[36] as well as fossils.[37]

CT may be enhanced by use of contrast agents containing elements of a higher atomic number than the surrounding flesh such as iodine or barium. Contrast agents for MRI are those which have paramagnetic properties, e.g. gadolinium and manganese.

Both CT and MRI scanners can generate multiple two-dimensional cross-sections (slices) of tissue and three-dimensional reconstructions. Unlike CT, which uses only X-ray attenuation to generate image contrast, MRI has a long list of properties that may be used to generate image contrast. By variation of scanning parameters, tissue contrast can be altered and enhanced in various ways to detect different features. (See Applications above.)

MRI can generate cross-sectional images in any plane (including oblique planes). In the past, CT was limited to acquiring images in the axial (or near axial) plane. The scans used to be called Computed *Axial* Tomography scans (CAT scans). However, the development of multi-detector CT scanners with near-isotropic resolution, allows the CT scanner to produce data that can be retrospectively reconstructed in any plane with minimal loss of image quality.

For purposes of tumor detection and identification in the brain, MRI is generally superior.[38] [39] [40] However, in the case of solid tumors of the abdomen and chest, CT is often preferred due to less motion artifact. Furthermore, CT usually is more widely available, faster, much less expensive, and may be less likely to require the person to be sedated or anesthetized.

MRI is also best suited for cases when a patient is to undergo the exam several times successively in the short term, because, unlike CT, it does not expose the patient to the hazards of ionizing radiation.

Economics of MRI

MRI equipment is expensive. 1.5 tesla scanners often cost between $1 million and $1.5 million USD. 3.0 tesla scanners often cost between $2 million and $2.3 million USD. Construction of MRI suites can cost up to $500,000 USD, or more, depending on project scope.

MRI scanners have been significant sources of revenue for healthcare providers in the US. This is because of favorable reimbursement rates from insurers and federal government programs. Insurance reimbursement is provided in two components, an equipment charge for the actual performance of the MRI scan and professional charge for the radiologist's review of the images and/or data. In the US Northeast, an equipment charge might be $3,500 and a professional charge might be $350.[41] Some insurance companies require preapproval of an MRI procedure as a condition for coverage.

In the US, the 2007 Deficit Reduction Act (DRA) significantly reduced reimbursement rates paid by federal insurance programs for the equipment component of many scans, shifting the economic landscape. Many private insurers have followed suit.

Safety

Death and injuries have occurred from projectiles created by the magnetic field, although relatively few compared to the millions of examinations administered.[42] [43] MRI makes use of powerful magnetic fields which, though they have not been demonstrated to cause direct biological damage, can interfere with metallic and electromechanical devices. Additional (small) risks are presented by the radio frequency systems, components or elements of the MRI system's operation, elements of the scanning procedure and medications that may be administered to facilitate MRI imaging.

There are many steps that the MRI patient and referring physician can take to help reduce the remaining risks, including providing a full, accurate and thorough medical history to the MRI provider.

Several of the specific MRI safety considerations are identified below:

Implants and foreign bodies

Pacemakers are generally considered an absolute contraindication towards MRI scanning, though highly specialized protocols have been developed to permit scanning of select pacing devices. Several cases of arrhythmia or death have been reported in patients with pacemakers who have undergone MRI scanning without appropriate precautions. Notably, the Medtronic company has received FDA approval for the first-ever clinical trial for a MR-Conditional pacemaker device, which has already received regulatory approval in Europe. Other electronic implants have varying contraindications, depending upon scanner technology, and implant properties, scanning protocols and anatomy being imaged.

Many other forms of medical or biostimulation implants may be contraindicated for MRI scans. These may include vagus nerve stimulators, implantable cardioverter-defibrillators, loop recorders, insulin pumps, cochlear implants, deep brain stimulators, and many others. Medical device patients should always present complete information (manufacturer, model, serial number and date of implantation) about all implants to both the referring physician and to the radiologist or technologist before entering the room for the MRI scan.

While these implants pose a current problem, scientists and manufacturers are working on improved designs which will further minimize the risks that MRI scans pose to medical device operations. One such development in the works is a nano-coating for implants intended to screen them from the radio frequency waves, helping to make MRI exams available to patients currently prohibited from receiving them. The current article [44] for this is from New Scientist.

Ferromagnetic foreign bodies (e.g. shell fragments), or metallic implants (e.g. surgical prostheses, aneurysm clips) are also potential risks, and safety aspects need to be considered on an individual basis. Interaction of the magnetic and radio frequency fields with such objects can lead to trauma due to movement of the object in the magnetic field, thermal injury from radio-frequency induction heating of the object, or failure of an implanted device. These issues are especially problematic when dealing with the eye. Most MRI centers require an orbital x-ray to be performed on anyone suspected of having metal fragments in their eyes, something not uncommon in metalworking.

Because of its non-ferromagnetic nature and poor electrical conductivity, titanium and its alloys are useful for long term implants and surgical instruments intended for use in image-guided surgery. In particular, not only is titanium safe from movement from the magnetic field, but artifacts around the implant are less frequent and less severe than with more ferromagnetic materials e.g. stainless steel. Artifacts from metal frequently appear as regions of empty space around the implant - frequently called 'black-hole artifact' e.g. a 3mm titanium alloy coronary stent may appear as a 5mm diameter region of empty space on MRI, whereas around a stainless steel stent, the artifact may extend for 10-20 mm or more.

In 2006, a new classification system for implants and ancillary clinical devices has been developed by ASTM International and is now the standard supported by the US Food and Drug Administration:

MR-Safe — The device or implant is completely non-magnetic, non-electrically conductive, and non-RF reactive, eliminating all of the primary potential threats during an MRI procedure.

MR Safe sign

MR-Conditional — A device or implant that may contain magnetic, electrically conductive or RF-reactive components that is safe for operations in proximity to the MRI, provided the conditions for safe operation are defined and observed (such as 'tested safe to 1.5 teslas' or 'safe in magnetic fields below 500 gauss in strength').

MR Conditional sign

> *MR-Unsafe* — Nearly self-explanatory, this category is reserved for objects that are significantly ferromagnetic and pose a clear and direct threat to persons and equipment within the magnet room.

MR Unsafe sign

Though the current classification system was originally developed for regulatory-approved medical devices, it is being applied to all manner of items, appliances and equipment intended for use in the MR environment.

In the case of pacemakers, the risk is thought to be primarily RF induction in the pacing electrodes/wires causing inappropriate pacing of the heart, rather than the magnetic field affecting the pacemaker itself. Much research and development is being undertaken, and many tools are being developed in order to predict the effects of the RF fields inside the body.

Patients who have been prescribed MRI exams who are concerned about safety may be interested in the 10 Questions To Ask Your MRI Provider [45].

MRI providers who wish to measure the degree to which they have effectively addressed the safety issues for patients and staff may be interested in the MRI Suite Safety Calculator [46] provided through a radiology website.

Projectile or missile effect

As a result of the very high strength of the magnetic field needed to produce scans (frequently up to 60,000 times the earth's own magnetic field effects), there are several incidental safety issues addressed in MRI facilities. Missile-effect accidents, where ferromagnetic objects are attracted to the center of the magnet, have resulted in injury and death.[47] [48] A video simulation of a fatal projectile effect accident [49] illustrates the extreme power that contemporary MRI equipment can exert on ferromagnetic objects.

In order to help reduce the risks of projectile accidents, ferromagnetic objects and devices are typically prohibited in proximity to the MRI scanner, with non-ferromagnetic versions of many tools and devices typically retained by the scanning facility. Patients undergoing MRI examinations are required to remove all metallic objects, often by changing into a gown or scrubs.

New ferromagnetic-only detection devices are proving highly effective in supplementing conventional screening techniques in many leading hospitals and imaging centers and are now recommended by the American College of Radiology's *Guidance Document for Safe MR Practices: 2007* [50], the United States' Veterans Administration's Design Guide [51] and the Joint Commission's Sentinel Event Alert #38 [52].

The magnetic field and the associated risk of missile-effect accidents remains a permanent hazard — as superconductive MRI magnets retain their magnetic field, even in the event of a power outage.

Radio frequency energy

A powerful radio transmitter is needed for excitation of proton spins. This can heat the body to the point of risk of hyperthermia in patients, particularly in obese patients or those with thermoregulation disorders. Several countries have issued restrictions on the maximum specific absorption rate that a scanner may produce.

Peripheral nerve stimulation (PNS)

The rapid switching on and off of the magnetic field gradients is capable of causing nerve stimulation. Volunteers report a twitching sensation when exposed to rapidly switched fields, particularly in their extremities. The reason the peripheral nerves are stimulated is that the changing field increases with distance from the center of the gradient coils (which more or less coincides with the center of the magnet). Note however that when imaging the head, the heart is far off-center and induction of even a tiny current into the heart must be avoided at all costs. Although PNS was not a problem for the slow, weak gradients used in the early days of MRI, the strong, rapidly-switched gradients used in techniques such as EPI, fMRI, diffusion MRI, etc. are indeed capable of inducing PNS. American and European regulatory agencies insist that manufacturers stay below specified dB/dt limits (dB/dt is the change in field per unit time) or else prove that no PNS is induced for any imaging sequence. As a result of dB/dt limitation, commercial MRI systems cannot use the full rated power of their gradient amplifiers.

Acoustic noise

Switching of field gradients causes a change in the Lorentz force experienced by the gradient coils, producing minute expansions and contractions of the coil itself. As the switching is typically in the audible frequency range, the resulting vibration produces loud noises (clicking or beeping). This is most marked with high-field machines and rapid-imaging techniques in which sound intensity can reach 120 dB(A) (equivalent to a jet engine at take-off) [53] .

Appropriate use of ear protection is essential for anyone inside the MRI scanner room during the examination.[54]

Cryogens

As described above in 'Scanner Construction And Operation', many MRI scanners rely on cryogenic liquids to enable superconducting capabilities of the electromagnetic coils within. Though the cryogenic liquids most frequently used are non-toxic, their physical properties present specific hazards.

An emergency shut-down of a superconducting electromagnet, an operation known as "quenching", involves the rapid boiling of liquid helium from the device. If the rapidly expanding helium cannot be dissipated through an external vent, sometimes referred to as 'quench pipe', it may be released into the scanner room where it may cause displacement of the oxygen and present a risk of asphyxiation.[55]

Liquid helium, the most commonly used cryogen in MRI, undergoes near explosive expansion as it changes from liquid to a gaseous state. Rooms built in support of superconducting MRI equipment should be equipped with pressure relief mechanisms[56] and an exhaust fan, in addition to the required quench pipe.

Since a quench results in rapid loss of all cryogens in the magnet, recommissioning the magnet is extremely expensive and time-consuming. Spontaneous quenches are uncommon, but may also be triggered by equipment malfunction, improper cryogen fill technique, contaminates inside the cryostat, or extreme magnetic or vibrational disturbances.

Contrast agents

The most commonly used intravenous contrast agents are based on chelates of gadolinium. In general, these agents have proved safer than the iodinated contrast agents used in X-ray radiography or CT. Anaphylactoid reactions are rare, occurring in approx. 0.03-0.1%.[57] Of particular interest is the lower incidence of nephrotoxicity, compared with iodinated agents, when given at usual doses—this has made contrast-enhanced MRI scanning an option for patients with renal impairment, who would otherwise not be able to undergo contrast-enhanced CT.[58]

Although gadolinium agents have proved useful for patients with renal impairment, in patients with severe renal failure requiring dialysis there is a risk of a rare but serious illness, nephrogenic systemic fibrosis, that may be linked to the use of certain gadolinium-containing agents. The most frequently linked is gadodiamide, but other agents have been linked too.[59] Although a causal link has not been definitively established, current guidelines in the United States are that dialysis patients should only receive gadolinium agents where essential, and that dialysis should be performed as soon as possible after the scan is complete, in order to remove the agent from the body promptly.[60] In Europe where more gadolinium-containing agents are available, a classification of agents according to potential risks has been released.[61] [62]

Pregnancy

No effects of MRI on the fetus have been demonstrated.[63] In particular, MRI avoids the use of ionizing radiation, to which the fetus is particularly sensitive. However, as a precaution, current guidelines recommend that pregnant women undergo MRI only when essential. This is particularly the case during the first trimester of pregnancy, as organogenesis takes place during this period. The concerns in pregnancy are the same as for MRI in general, but the fetus may be more sensitive to the effects—particularly to heating and to noise. However, one additional concern is the use of contrast agents; gadolinium compounds are known to cross the placenta and enter the fetal bloodstream, and it is recommended that their use be avoided.

Despite these concerns, MRI is rapidly growing in importance as a way of diagnosing and monitoring congenital defects of the fetus because it can provide more diagnostic information than ultrasound and it lacks the ionizing radiation of CT. MRI without contrast agents is the imaging mode of choice for pre-surgical, in-utero diagnosis and evaluation of fetal tumors, primarily teratomas, facilitating open fetal surgery, other fetal interventions, and planning for procedures (such as the EXIT procedure) to safely deliver and treat babies whose defects would otherwise be fatal.

Claustrophobia and discomfort

Due to the construction of some MRI scanners, they can be potentially unpleasant to lie in. Older models of closed bore MRI systems feature a fairly long tube or tunnel. The part of the body being imaged needs to lie at the center of the magnet which is at the absolute center of the tunnel. Because scan times on these older scanners may be long (occasionally up to 40 minutes for the entire procedure), people with even mild claustrophobia are sometimes unable to tolerate an MRI scan without management. Modern scanners may have larger bores (up to 70 cm) and scan times are shorter. This means that claustrophobia is less of an issue, and many patients now find MRI an innocuous and easily tolerated procedure.

Nervous patients may still find the following strategies helpful:

- Advance preparation
  - visiting the scanner to see the room and practice lying on the table
  - visualization techniques
  - chemical sedation
  - general anesthesia
- Coping while inside the scanner
  - holding a "panic button"
  - closing eyes as well as covering them (e.g. washcloth, eye mask)
  - listening to music on headphones or watching a movie with a Head-mounted display while in the machine
  - Scan Rooms with lighting, sound and images on the wall. Some rooms come with images on the walls or ceiling.

Alternative scanner designs, such as open or upright systems, can also be helpful where these are available. Though open scanners have increased in popularity, they produce inferior scan quality because they operate at lower magnetic fields than closed scanners. However, commercial 1.5 Tesla open systems have recently become available, providing much better image quality than previous lower field strength open models[64].

For babies and young children chemical sedation or general anesthesia are the norm, as these subjects cannot be instructed to hold still during the scanning session. Obese patients and pregnant women may find the MRI machine to be a tight fit. Pregnant women may also have difficulty lying on their backs for an hour or more without moving.

Acoustic noise associated with the operation of an MRI scanner can also exacerbate the discomfort associated with the procedure.

Nephrogenic systemic fibrosis (NSF) or Nephrogenic fibrosing dermopathy is a rare and serious syndrome that involves fibrosis of skin, joints, eyes, and internal organs. Its cause is not fully understood, but it seems to be associated with exposure to gadolinium (which is frequently used as a contrast substance for MRIs) in patients with severe kidney failure.

Guidance

Safety issues, including the potential for biostimulation device interference, movement of ferromagnetic bodies, and incidental localized heating, have been addressed in the American College of Radiology's *White Paper on MR Safety* which was originally published in 2002 and expanded in 2004. The *ACR White Paper on MR Safety* has been rewritten and was released early in 2007 under the new title *ACR Guidance Document for Safe MR*

Practices [50].

In December 2007, the Medicines in Healthcare product Regulation Agency (MHRA), a UK healthcare regulatory body, issued their *Safety Guidelines for Magnetic Resonance Imaging Equipment in Clinical Use* [65].

In February 2008, the Joint Commission, a US healthcare accrediting organization, issued a Sentinel Event Alert #38 [52], their highest patient safety advisory, on MRI safety issues.

In July 2008, the United States Veterans Administration, a federal governmental agency serving the healthcare needs of former military personnel, issued a substantial revision to their *MRI Design Guide* [66] which includes physical or facility safety considerations.

The European Physical Agents Directive

The European Physical Agents (Electromagnetic Fields) Directive is legislation adopted in European legislature. Originally scheduled to be required by the end of 2008, each individual state within the European Union must include this directive in its own law by the end of 2012. Some member nations passed complying legislation and are now attempting to repeal their state laws in expectation that the final version of the EU Physical Agents Directive will be substantially revised prior to the revised adoption date.

The directive applies to occupational exposure to electromagnetic fields (not medical exposure) and was intended to limit workers' acute exposure to strong electromagnetic fields, as may be found near electricity substations, radio or television transmitters or industrial equipment. However, the regulations impact significantly on MRI, with separate sections of the regulations limiting exposure to static magnetic fields, changing magnetic fields and radio frequency energy. Field strength limits are given which may not be exceeded for any period of time. An employer may commit a criminal offense by allowing a worker to exceed an exposure limit if that is how the Directive is implemented in a particular Member State.

The Directive is based on the international consensus of established effects of exposure to electromagnetic fields, and in particular the advice of the European Commissions's advisor, the International Commission on Non-Ionizing Radiation Protection (ICNIRP). The aims of the Directive, and the ICNIRP guidelines upon which it is based, are to prevent exposure to potentially harmful fields. The actual limits in the Directive are very similar to the limits advised by the Institute of Electrical and Electronics Engineers, with the exception of the frequencies produced by the gradient coils, where the IEEE limits are significantly higher.

Many Member States of the EU already have either specific EMF regulations or (as in the UK) a general requirement under workplace health and safety legislation to protect workers against electromagnetic fields. In almost all cases the existing regulations are aligned with the ICNIRP limits so that the Directive should, in theory, have little impact on any employer already meeting their legal responsibilities.

The introduction of the Directive has brought to light an existing potential issue with occupational exposures to MRI fields. There are at present very few data on the number or types of MRI practice that might lead to exposures in excess of the levels of the Directive.[67] [68] There is a justifiable concern amongst MRI practitioners that if the Directive were to be enforced more vigorously than existing legislation, the use of MRI might be restricted, or working practices of MRI personnel might have to change.

In the initial draft a limit of static field strength to 2 T was given. This has since been removed from the regulations, and whilst it is unlikely to be restored as it was without a

strong justification, some restriction on static fields may be reintroduced after the matter has been considered more fully by ICNIRP. The effect of such a limit might be to restrict the installation, operation and maintenance of MRI scanners with magnets of 2 T and stronger. As the increase in field strength has been instrumental in developing higher resolution and higher performance scanners, this would be a significant step back. This is why it is unlikely to happen without strong justification.

Individual government agencies and the European Commission have now formed a working group to examine the implications on MRI and to try to address the issue of occupational exposures to electromagnetic fields from MRI.

2003 Nobel Prize

Reflecting the fundamental importance and applicability of MRI in the medical field, Paul Lauterbur of the University of Illinois at Urbana-Champaign and Sir Peter Mansfield of the University of Nottingham were awarded the 2003 Nobel Prize in Physiology or Medicine for their "discoveries concerning magnetic resonance imaging". The Nobel Prize committee acknowledged Lauterbur's insight of using magnetic field gradients to introduce spatial localization, a discovery that allowed rapid acquisition of 2D images. Sir Peter Mansfield was credited with introducing the mathematical formalism and developing techniques for efficient gradient utilization and fast imaging. The actual research by Paul Lauterbur was done almost 30 years ago at Stony Brook University in Stony Brook, NY.

The award was vigorously protested by Raymond Vahan Damadian, founder of FONAR Corporation, who claimed that he was the inventor of MRI, and that Lauterbur and Mansfield had merely refined the technology.[3] An ad hoc group, called "The Friends of Raymond Damadian", took out full-page advertisements in the *New York Times* and *The Washington Post* entitled "The Shameful Wrong That Must Be Righted", demanding that he be awarded at least a share of the Nobel Prize [69] . Also, in a letter to *Physics Today*, Herman Carr pointed out his own early use of field gradients for one-dimensional MR imaging[70] .

See also

- Earth's field NMR (EFNMR)
- Electron-spin resonance (spin physics)
- History of brain imaging
- Medical imaging
- Magnetic immunoassay

- Nuclear magnetic resonance (NMR)
- Relaxation
- Robinson oscillator
- Rabi cycle

- Magnetic resonance microscopy
- Magnetic Particle Imaging (MPI)
- Magnetic resonance elastography
- Neuroimaging software
- Nephrogenic fibrosing dermopathy
- Nobel Prize controversies

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External links

- BIGS-animation (http://www.bigs.de/BLH/en/index.php?option=com_content&view=category&layout=blog&id=100&Itemid=268) - Physics of MRI like spin, modification of spin or pulse sequences

- MDCT (http://www.mdct.com.au) - Free Radiology Resource For Radiographers, Radiologists and Technical Assistants

- A Guided Tour of MRI: An introduction for laypeople (http://www.magnet.fsu.edu/education/tutorials/magnetacademy/mri/) National High Magnetic Field Laboratory

- Joseph P. Hornak, Ph.D. The Basics of MRI (http://www.cis.rit.edu/htbooks/mri/). *Underlying physics and technical aspects*.

- Video: What to Expect During Your MRI Exam (http://www.imrser.org/PatientVideo.html) from the Institute for Magnetic Resonance Safety, Education, and Research (IMRSER)

- 3D Animation Movie about MRI Exam (http://www.patiencys.com/MRI/)

- Interactive Flash Animation on MRI (http://www.e-mri.org) - *Online Magnetic Resonance Imaging physics and technique course*

- International Society for Magnetic Resonance in Medicine (http://www.ismrm.org)

- Article on helium scarcity and potential effects on NMR and MRI communities (http://www.ebyte.it/stan/blog.html#08Feb29)

- Danger of objects flying into the scanner (http://www.simplyphysics.com/flying_objects.html)

- Video compiled of MRI scans showing arachnoid cyst (http://www.youtube.com/watch?v=PF_mDsdxSsg)

Neuroimaging

Neuroimaging includes the use of various techniques to either directly or indirectly image the structure, function/pharmacology of the brain. It is a relatively new discipline within medicine and neuroscience/psychology.

Para-sagittal MRI of the head in a patient with benign familial macrocephaly.

Overview

Neuroimaging falls into two broad categories:

- Structural imaging, which deals with the structure of the brain and the diagnosis of gross (large scale) intracranial disease (such as tumor), and injury, and
- functional imaging, which is used to diagnose metabolic diseases and lesions on a finer scale (such as Alzheimer's disease) and also for neurological and cognitive psychology research and building brain-computer interfaces.

Functional imaging enables, for example, the processing of information by centers in the brain to be visualized directly. Such processing causes the involved area of the brain to increase metabolism and "light up" on the scan.

3-D MRI of a section of the head.

History

In 1918 the American neurosurgeon Walter Dandy introduced the technique of ventriculography. X-ray images of the ventricular system within the brain were obtained by injection of filtered air directly into one or both lateral ventricles of the brain. Dandy also observed that air introduced into the subarachnoid space via lumbar spinal puncture could enter the cerebral ventricles and also demonstrate the cerebrospinal fluid compartments around the base of the brain and over its surface. This technique was called pneumoencephalography.

In 1927 Egas Moniz, professor of neurology in Lisbon and recipient of the Nobel Prize for Physiology or Medicine in 1949, introduced cerebral angiography, whereby both normal and abnormal blood vessels in and around the brain could be visualized with great accuracy.

In the early 1970s, Allan McLeod Cormack and Godfrey Newbold Hounsfield introduced computerized axial tomography (CAT or CT scanning), and ever more detailed anatomic images of the brain became available for diagnostic and research purposes. Cormack and Hounsfield won the 1979 Nobel Prize for Physiology or Medicine for their work. Soon after the introduction of CAT in the early 1980s, the development of radioligands allowed single photon emission computed tomography (SPECT) and positron emission tomography (PET)

of the brain.

More or less concurrently, magnetic resonance imaging (MRI or MR scanning) was developed by researchers including Peter Mansfield and Paul Lauterbur, who were awarded the Nobel Prize for Physiology or Medicine in 2003. In the early 1980s MRI was introduced clinically, and during the 1980s a veritable explosion of technical refinements and diagnostic MR applications took place. Scientists soon learned that the large blood flow changes measured by PET could also be imaged by the correct type of MRI. Functional magnetic resonance imaging (fMRI) was born, and since the 1990s, fMRI has come to dominate the brain mapping field due to its low invasiveness, lack of radiation exposure, and relatively wide availability. As noted above fMRI is also beginning to dominate the field of stroke treatment.

In early 2000s the field of neuroimaging reached the stage where limited practical applications of functional brain imaging have become feasible. The main application area is crude forms of brain-computer interface.

Brain imaging techniques

Computed Axial Tomography

Computed Tomography (CT) or *Computed Axial Tomography* (CAT) scanning uses a series of x-rays of the head taken from many different directions. Typically used for quickly viewing brain injuries, CT scanning uses a computer program that performs a numerical integral calculation (the inverse Radon transform) on the measured x-ray series to estimate how much of an x-ray beam is absorbed in a small volume of the brain. Typically the information is presented as cross sections of the brain.[1]

In approximation, the denser a material is, the whiter a volume of it will appear on the scan (just as in the more familiar "flat" X-rays). CT scans are primarily used for evaluating swelling from tissue damage in the brain and in assessment of ventricle size. Modern CT scanning can provide reasonably good images in a matter of minutes.

Diffuse Optical Imaging

Diffuse Optical Imaging (DOI) or Diffuse Optical Tomography (DOT) is a medical imaging modality which uses near infrared light to generate images of the body. The technique measures the optical absorption of haemoglobin, and relies on the absorption spectrum of haemoglobin varying with its oxygenation status.

Event Related Optical Signal

Event Related Optical Signal (EROS) is a brain-scanning technique which uses infrared light through optical fibers to measure changes in optical properties of active areas of the cerebral cortex. Whereas techniques such as diffuse optical imaging (DOT) and near infrared spectroscopy (NIRS) measure optical absorption of haemoglobin, and thus are based on blood flow, EROS takes advantage of the scattering properties of the neurons themselves, and thus provides a much more direct measure of cellular activity. EROS can pinpoint activity in the brain within millimeters (spatially) and within milliseconds (temporally). Its biggest downside is the inability to detect activity more than a few centimeters deep. EROS is a new, relatively inexpensive technique that is non-invasive to the test subject. It was developed at the University of Illinois at Urbana-Champaign where

it is now used in the Cognitive Neuroimaging Laboratory of Dr. Gabriele Gratton and Dr. Monica Fabiani.

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) uses magnetic fields and radio waves to produce high quality two- or three-dimensional images of brain structures without use of ionizing radiation (X-rays) or radioactive tracers. During an MRI, a large cylindrical magnet creates a magnetic field around the head of the patient through which radio waves are sent. When the magnetic field is imposed, each point in space has a unique radio frequency at which the signal is received and transmitted (Preuss). Sensors read the frequencies and a computer uses the information to construct an image. The detection mechanisms are so precise that changes in structures over time can be detected.

Sagittal MRI slice at the midline.

Using MRI, scientists can create images of both surface and subsurface structures with a high degree of anatomical detail. MRI scans can produce cross sectional images in any direction from top to bottom, side to side, or front to back. The problem with original MRI technology was that while it provides a detailed assessment of the physical appearance, water content, and many kinds of subtle derangements of structure of the brain (such as inflammation or bleeding), it fails to provide information about the metabolism of the brain (i.e. how actively it is functioning) at the time of imaging. A distinction is therefore made between "MRI imaging" and "functional MRI imaging" (fMRI), where MRI provides only structural information on the brain while fMRI yields both structural and functional data.

Functional Magnetic Resonance Imaging

Functional Magnetic Resonance Imaging (fMRI) relies on the paramagnetic properties of oxygenated and deoxygenated hemoglobin to see images of changing blood flow in the brain associated with neural activity. This allows images to be generated that reflect which brain structures are activated (and how) during performance of different tasks.

Most fMRI scanners allow subjects to be presented with different visual images, sounds and touch stimuli, and to make different actions such as pressing a button or moving a joystick. Consequently, fMRI can be used to reveal brain structures and processes associated with perception, thought and action. The resolution of fMRI is about 2-3 millimeters at present, limited by the spatial spread of the hemodynamic response to neural activity. It has largely superseded PET for the study of brain activation patterns. PET, however, retains the significant advantage of being able to identify specific

Axial MRI slice at the level of the basal ganglia, showing fMRI BOLD signal changes overlayed in red (increase) and blue (decrease) tones.

brain receptors (or transporters) associated with particular neurotransmitters through its ability to image radiolabelled receptor "ligands" (receptor ligands are any chemicals that stick to receptors).

As well as research on healthy subjects, fMRI is increasingly used for the medical diagnosis of disease. Because fMRI is exquisitely sensitive to blood flow, it is extremely sensitive to early changes in the brain resulting from ischemia (abnormally low blood flow), such as the changes which follow stroke. Early diagnosis of certain types of stroke is increasingly important in neurology, since substances which dissolve blood clots may be used in the first few hours after certain types of stroke occur, but are dangerous to use afterwards. Brain changes seen on fMRI may help to make the decision to treat with these agents. With between 72% and 90% accuracy where chance would achieve 0.8%,[2] fMRI techniques can decide which of a set of known images the subject is viewing.[3]

MagnetoEncephaloGraphy

Magnetoencephalography (MEG) is an imaging technique used to measure the magnetic fields produced by electrical activity in the brain via extremely sensitive devices such as superconducting quantum interference devices (SQUIDs). MEG offers a very direct measurement neural electrical activity (compared to fMRI for example) with very high temporal resolution but relatively low spatial resolution. The advantage of measuring the magnetic fields produced by neural activity is that they are not distorted by surrounding tissue, unlike the electric fields measured by EEG (particularly the skull and scalp).

There are many uses for the MEG, including assisting surgeons in localizing a pathology, assisting researchers in determining the function of various parts of the brain, neurofeedback, and others.
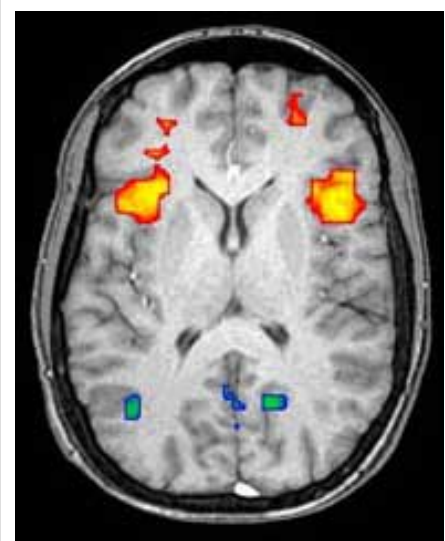
Positron Emission Tomography

Positron Emission Tomography (PET) measures emissions from radioactively labeled metabolically active chemicals that have been injected into the bloodstream. The emission data are computer-processed to produce 2- or 3-dimensional images of the distribution of the chemicals throughout the brain. [4] The positron emitting radioisotopes used are produced by a cyclotron, and chemicals are labeled with these radioactive atoms. The labeled compound, called a *radiotracer*, is injected into the bloodstream and eventually makes its way to the brain. Sensors in the PET scanner detect the radioactivity as the compound accumulates in various regions of the brain. A computer uses the data gathered by the sensors to create multicolored 2- or 3-dimensional images that

PET scan of a normal 20-year-old brain.

show where the compound acts in the brain. Especially useful are a wide array of ligands used to map different aspects of neurotransmitter activity, with by far the most commonly used PET tracer being a labeled form of glucose (see FDG).

The greatest benefit of PET scanning is that different compounds can show blood flow and oxygen and glucose metabolism in the tissues of the working brain. These measurements reflect the amount of brain activity in the various regions of the brain and allow to learn more about how the brain works. PET scans were superior to all other metabolic imaging methods in terms of resolution and speed of completion (as little as 30 seconds), when they first became available. The improved resolution permitted better study to be made as to the area of the brain activated by a particular task. The biggest drawback of PET scanning is that because the radioactivity decays rapidly, it is limited to monitoring short tasks. [5] Before fMRI technology came online, PET scanning was the preferred method of functional (as opposed to structural) brain imaging, and it still continues to make large contributions to neuroscience.

PET scanning is also used for diagnosis of brain disease, most notably because brain tumors, strokes, and neuron-damaging diseases which cause dementia (such as Alzheimer's disease) all cause great changes in brain metabolism, which in turn causes easily detectable changes in PET scans. PET is probably most useful in early cases of certain dementias (with classic examples being Alzheimer's disease and Pick's disease) where the early damage is too diffuse and makes too little difference in brain volume and gross structure to change CT and standard MRI images enough to be able to reliably differentiate it from the "normal" range of cortical atrophy which occurs with aging (in many but not all) persons, and which does *not* cause clinical dementia.

Single Photon Emission Computed Tomography

Single Photon Emission Computed Tomography (SPECT) is similar to PET and uses gamma ray emitting radioisotopes and a gamma camera to record data that a computer uses to construct two- or three-dimensional images of active brain regions[6] SPECT relies on an injection of radioactive tracer, which is rapidly taken up by the brain but does not redistribute. Uptake of SPECT agent is nearly 100% complete within 30 – 60s, reflecting cerebral blood flow (CBF) at the time of injection. These properties of SPECT make it particularly well suited for epilepsy imaging, which is usually made difficult by problems with patient movement and variable seizure types. SPECT provides a "snapshot" of cerebral blood flow since scans can be acquired after seizure termination (so long as the radioactive tracer was injected at the time of the seizure). A significant limitation of SPECT is its poor resolution (about 1 cm) compared to that of MRI.

Like PET, SPECT also can be used to differentiate different kinds of disease processes which produce dementia, and it is increasingly used for this purpose. Neuro-PET has a disadvantage of requiring use of tracers with half-lives of at most 110 minutes, such as FDG. These must be made in a cyclotron, and are expensive or even unavailable if necessary transport times are prolonged more than a few half-lives. SPECT, however, is able to make use of tracers with much longer half-lives, such as technetium-99m, and as a result, is far more widely available.

See also

- Brain mapping
- Functional neuroimaging
- functional near-infrared imaging
- History of brain imaging
- Human Cognome Project
- Magnetic resonance imaging
- Magnetoencephalography
- Medical imaging
- Neuroimaging software
- Statistical parametric mapping
- Transcranial magnetic stimulation
- Voxel-based morphometry
- Physioscan

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[4] Nilsson, page 57

[5] Nilson, pg. 60

[6] Philip Ball *Brain Imaging Explained*

Further reading

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External links

- The Whole Brain Atlas @ Harvard (http://www.med.harvard.edu/AANLIB/home.html)
- The McConnell Brain Imaging Center, McGill University (http://www2.bic.mni.mcgill.ca/)
- The American Society of Neuroimaging (ASN) (http://www.asnweb.org/).
- UCLA Neuroimaging Training Program (http://www.brainmapping.org/NITP).
- Laboratory of Neuro Imaging (http://www.loni.ucla.edu/) at UCLA
- A Neuroimaging portal (http://www.mri-tutorial.com/)
- BrainMapping.org, *a free BrainMapping community information portal* (http://www.brainmapping.org/)
- Lecture notes on mathematical aspects of neuroimaging (http://www.fil.ion.ucl.ac.uk/~wpenny/mbi/) by Will Penny, University College London
- "Transcranial Magnetic Stimulation" (http://www.ai.mit.edu/projects/medical-vision/surgery/tms.html). by Michael Leventon in association with MIT AI Lab.
- *Foundations of fMRI* (http://www.ee.duke.edu/~jshorey/MRIHomepage/MRImain.html) by Jamie Shorey.
- International Society for Neuroimaging in Psychiatry (ISNIP) (http://www.isnip.org/)

Computed tomography

]**Computed tomography (CT)** is a medical imaging method employing tomography. Digital geometry processing is used to generate a three-dimensional image of the inside of an object from a

A Multislice CT Scanner:
[http://www.toshiba-medical.eu/upload/CT/AquilionONE/System%20Images/AQ1Enlarge.jpg
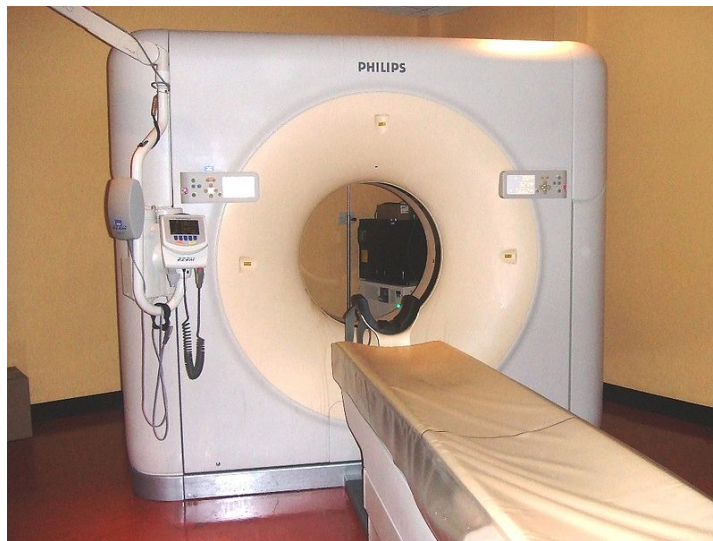
large series of two-dimensional X-ray images taken around a single axis of rotation. The word "tomography" is derived from the Greek *tomos* (slice) and *graphein* (to write). Computed tomography was originally known as the "EMI scan" as it was developed at a research branch of EMI, a company best known today for its music and recording business. It was later known as **computed axial tomography** (CAT or CT scan) and **body section röntgenography**.

CT produces a volume of data which can be manipulated, through a process known as "windowing", in order to demonstrate various bodily structures based on their ability to block the X-ray/Röntgen beam. Although historically the images generated were in the axial or transverse plane, orthogonal to the long axis of the body, modern scanners allow this volume of data to be reformatted in various planes or even as volumetric (3D) representations of structures. Although most common in medicine, CT is also used in other fields, such as nondestructive materials testing. Another example is the DigiMorph project at the University of Texas at Austin which uses a CT scanner to study biological and paleontological specimens.

History

In the early 1900s, the Italian radiologist Alessandro Vallebona proposed a method to represent a single slice of the body on the radiographic film. This method was known as tomography. The idea is based on simple principles of projective geometry: moving synchronously and in opposite directions the X-ray tube and the film, which are connected together by a rod whose pivot point is the focus; the image created by the points on the focal plane appears sharper, while the images of the other points annihilate as noise. This is only marginally effective, as blurring occurs only in the "x" plane. There are also more complex devices which can move in more than one plane and perform more effective blurring.

Tomography had been one of the pillars of radiologic diagnostics until the late 1970s, when the availability of minicomputers and of the transverse axial scanning method, this last due to the work of Godfrey Hounsfield and South African born Allan McLeod Cormack, gradually supplanted it as the modality of CT.

The first commercially viable CT scanner was invented by Sir Godfrey Hounsfield in Hayes, United Kingdom at EMI Central Research Laboratories using X-rays. Hounsfield conceived his idea in 1967,[1] and it was publicly announced in 1972. Allan McLeod Cormack of Tufts University in Massachusetts independently invented a similar process, and both Hounsfield and Cormack shared the 1979 Nobel Prize in Medicine.[2]

The original 1971 prototype took 160 parallel readings through 180 angles, each 1° apart, with each scan taking a little over five minutes. The images from these scans took 2.5 hours to be processed by algebraic reconstruction techniques on a large computer. The scanner had a single photomultiplier detector, and operated on the Translate/Rotate principle.

The prototype CT scanner

It has been claimed that thanks to the success of The Beatles, EMI could fund research and build early models for medical use.[3] The first production X-ray CT machine (in fact called the "EMI-Scanner") was limited to making tomographic sections of the brain, but acquired the image data in about 4 minutes (scanning two adjacent slices), and the computation time (using a Data General Nova minicomputer) was about 7 minutes per picture. This scanner required the use of a water-filled Perspex tank with a pre-shaped rubber "head-cap" at the front, which enclosed the patient's head. The water-tank was used to reduce the dynamic range of the radiation reaching the detectors (between scanning outside the head compared with scanning through the bone of the skull). The images were relatively low resolution, being composed of a matrix of only 80 x 80 pixels. The first EMI-Scanner was installed in Atkinson Morley Hospital in Wimbledon, England, and the first patient brain-scan was made with it in 1972.

In the U.S., the first installation was at the Mayo Clinic. As a tribute to the impact of this system on medical imaging the Mayo Clinic has an EMI scanner on display in the Radiology Department.

The first CT system that could make images of any part of the body and did not require the "water tank" was the ACTA (Automatic Computerized Transverse Axial) scanner designed by Robert S. Ledley, DDS at Georgetown University. This machine had 30 photomultiplier tubes as detectors and completed a scan in only 9 translate/rotate cycles, much faster than the EMI-scanner.

A historic EMI-Scanner

It used a DEC PDP11/34 minicomputer both to operate the servo-mechanisms and to acquire and process the images. The Pfizer drug company acquired the prototype from the university, along with rights to manufacture it. Pfizer then began making copies of the prototype, calling it the "200FS" (FS meaning Fast Scan), which were selling as fast as they could make them. This unit produced images in a 256x256 matrix, with much better definition than the EMI-Scanner's 80x80
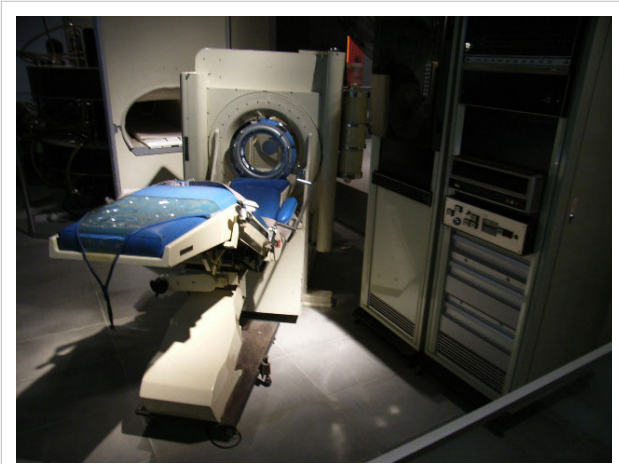
Previous studies

Tomography

A form of tomography can be performed by moving the X-ray source and detector during an exposure. Anatomy at the target level remains sharp, while structures at different levels are blurred. By varying the extent and path of motion, a variety of effects can be obtained, with variable depth of field and different degrees of blurring of 'out of plane' structures.[4] :25

Although largely obsolete, conventional tomography is still used in specific situations such as dental imaging (orthopantomography) or in intravenous urography.

Tomosynthesis

Digital tomosynthesis combines digital image capture and processing with simple tube/detector motion as used in conventional radiographic tomography. Although there are some similarities to CT, it is a separate technique. In CT, the source/detector makes a complete 360-degree rotation about the subject obtaining a complete set of data from which images may be reconstructed. In digital tomosynthesis, only a small rotation angle (e.g., 40 degrees) with a small number of discrete exposures (e.g., 10) are used. This incomplete set of data can be digitally processed to yield images similar to conventional tomography with a limited depth of field. However, because the image processing is digital, a series of slices at different depths and with different thicknesses can be reconstructed from the same acquisition, saving both time and radiation exposure.

Because the data acquired is incomplete, tomosynthesis is unable to offer the extremely narrow slice widths that CT offers. However, higher resolution detectors can be used, allowing very-high in-plane resolution, even if the Z-axis resolution is poor. The primary

interest in tomosynthesis is in breast imaging, as an extension to mammography, where it may offer better detection rates with little extra increase in radiation exposure.

Reconstruction algorithms for tomosynthesis are significantly different from conventional CT, because the conventional filtered back projection algorithm requires a complete set of data. Iterative algorithms based upon expectation maximization are most commonly used, but are extremely computationally intensive. Some manufacturers have produced practical systems using off-the-shelf GPUs to perform the reconstruction.

Diagnostic use

Since its introduction in the 1970s, CT has become an important tool in medical imaging to supplement X-rays and medical ultrasonography. Although it is still quite expensive, it is the gold standard in the diagnosis of a large number of different disease entities. It has more recently begun to also be used for preventive medicine or screening for disease, for example CT colonography for patients with a high risk of colon cancer. Although a number of institutions offer full-body scans for the general population, this practice remains controversial due to its lack of proven benefit, cost, radiation exposure, and the risk of finding 'incidental' abnormalities that may trigger additional investigations.

Head

CT scanning of the head is typically used to detect:

1. bleeding, brain injury and skull fractures
2. bleeding due to a ruptured/leaking aneurysm in a patient with a sudden severe headache
3. a blood clot or bleeding within the brain shortly after a patient exhibits symptoms of a stroke
4. a stroke
5. brain tumors
6. enlarged brain cavities in patients with hydrocephalus
7. diseases/malformations of the skull
8. evaluate the extent of bone and soft tissue damage in patients with facial trauma, and planning surgical reconstruction
9. diagnose diseases of the temporal bone on the side of the skull, which may be causing hearing problems

A head CT showing displacement of the ventricles (the dark structures) which are normally in the midline.

10. determine whether inflammation or other changes are present in the paranasal sinuses
11. plan radiation therapy for cancer of the brain or other tissues
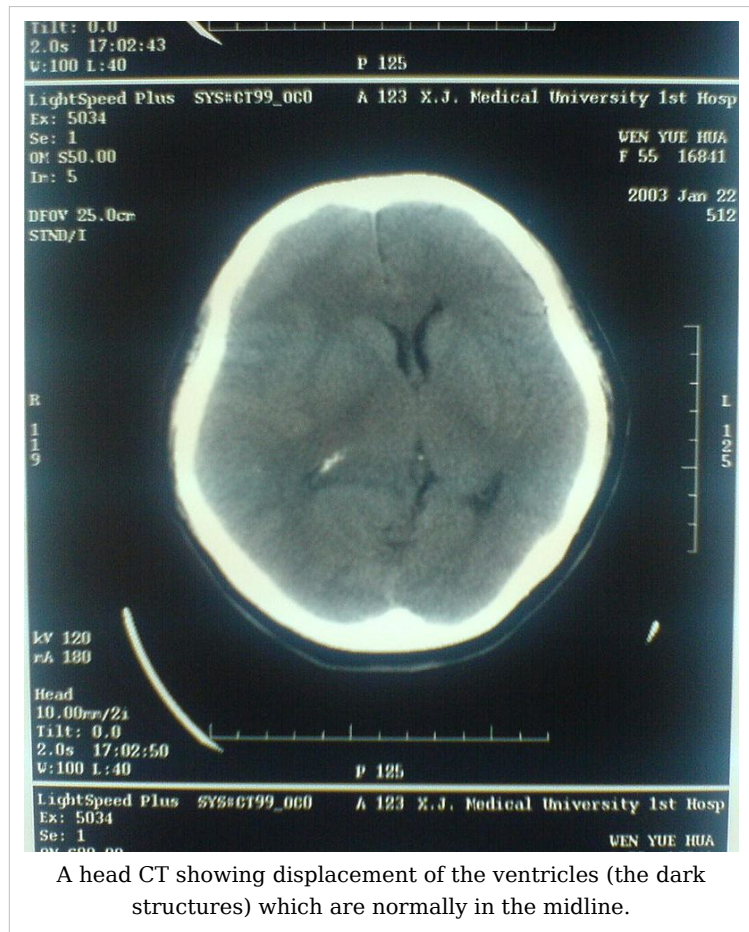
12. guide the passage of a needle used to obtain a tissue sample (biopsy) from the brain
13. assess aneurysms or arteriovenous malformations

Chest

CT can be used for detecting both acute and chronic changes in the lung parenchyma, that is, the internals of the lungs. It is particularly relevant here because normal two dimensional x-rays do not show such defects. A variety of different techniques are used depending on the suspected abnormality. For evaluation of chronic interstitial processes (emphysema, fibrosis, and so forth), thin sections with high spatial frequency reconstructions are used - often scans are performed both in inspiration and expiration. This special technique is called High Resolution CT (HRCT). HRCT is normally done with thin section with skipped areas between the thin sections. Therefore it produces a sampling of the lung and not continuous images. Continuous images are provided in a standard CT of the chest.

For detection of airspace disease (such as pneumonia) or cancer, relatively thick sections and general purpose image reconstruction techniques may be adequate. IV contrast may also be used as it clarifies the anatomy and boundaries of the great vessels and improves assessment of the mediastinum and hilar regions for lymphadenopathy; this is particularly important for accurate assessment of cancer.

CT angiography of the chest is also becoming the primary method for detecting pulmonary embolism (PE) and aortic dissection, and requires accurately timed rapid injections of contrast (Bolus Tracking) and high-speed helical scanners. CT is the standard method of evaluating abnormalities seen on chest X-ray and of following findings of uncertain acute significance.

More than 62 million scans are ordered each year, according to the 2007 New England Journal of Medicine study. 31% of 62 million (19,2 million) is used for lung CT's.

Pulmonary angiogram

CT pulmonary angiogram (CTPA) is a medical diagnostic test used to diagnose pulmonary embolism (PE). It employs computed tomography to obtain an image of the pulmonary arteries.

It is a preferred choice of imaging in the diagnosis of PE due to its minimally invasive nature for the patient, whose only requirement for the scan is a cannula (usually a 20G).

MDCT (multi detector CT) scanners give the optimum resolution and image quality for this test. Images are usually taken on a 0.625 mm slice thickness, although 2 mm is sufficient. 50 - 100 mls of contrast is given to the patient at a rate of 4 ml/s. The tracker/locator is placed at the level of the Pulmonary Arteries, which sit roughly at the level of the carina. Images are acquired with the maximum intensity of radio-opaque contrast in the Pulmonary Arteries. This is done using bolus tracking.

CT machines are now so sophisticated that the test can be done with a patient visit of 5 minutes with an approximate scan time of only 5 seconds or less.

A normal CTPA scan will show the contrast filling the pulmonary vessels, looking bright white. Ideally the aorta should be empty of contrast, to reduce any partial volume artifact which may result in a false positive. Any mass filling defects, such as an embolus, will appear dark in place of the contrast, filling / blocking the space where blood should be flowing into the lungs.

Example of a CTPA, demonstrating a saddle embolus (dark horizontal line) occluding the pulmonary arteries (bright white triangle)

Cardiac

With the advent of subsecond rotation combined with multi-slice CT (up to 64-slice), high resolution and high speed can be obtained at the same time, allowing excellent imaging of the coronary arteries (cardiac CT angiography). Images with an even higher temporal resolution can be formed using retrospective ECG gating. In this technique, each portion of the heart is imaged more than once while an ECG trace is recorded. The ECG is then used to correlate the CT data with their corresponding phases of cardiac contraction. Once this correlation is complete, all data that were recorded while the heart was in motion (systole) can be ignored and images can be made from the remaining data that happened to be acquired while the heart was at rest (diastole). In this way, individual frames in a cardiac CT investigation have a better temporal resolution than the shortest tube rotation time.

Because the heart is effectively imaged more than once (as described above), cardiac CT angiography results in a relatively high radiation exposure around 12 mSv. For the sake of comparison, a chest X-ray carries a dose of approximately 0.02[5] to 0.2 mSv and natural background radiation exposure is around 0.01 mSv/day. Thus, cardiac CTA is equivalent to approximately 100-600 chest X-rays or over 3 years worth of natural background radiation. Methods are available to decrease this exposure, however, such as prospectively decreasing radiation output based on the concurrently acquired ECG (aka tube current modulation.) This can result in a significant decrease in radiation exposure, at the risk of compromising image quality if there is any arrhythmia during the acquisition. The significance of radiation doses in the diagnostic imaging range has not been proven, although the possibility of inducing an increased cancer risk across a population is a source of significant concern. This potential risk must be weighed against the competing risk of not performing a test and potentially not diagnosing a significant health problem such as coronary artery disease.

It is uncertain whether this modality will replace invasive coronary catheterization. Currently, it appears that the greatest utility of cardiac CT lies in ruling out coronary artery disease rather than ruling it in. This is because the test has a high sensitivity (greater than 90%) and thus a negative test result means that a patient is very unlikely to have coronary artery disease and can be worked up for other causes of their chest symptoms. This is
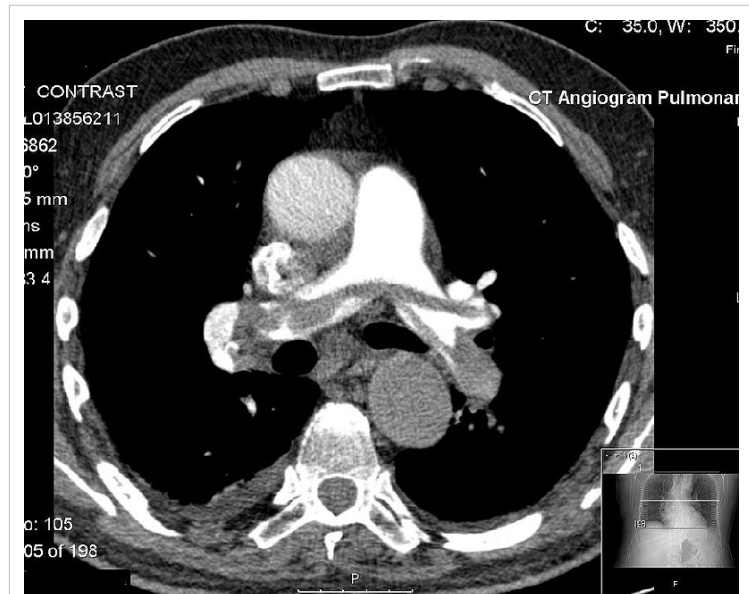
termed a high negative predictive value. A positive result is less conclusive and often will be confirmed (and possibly treated) with subsequent invasive angiography. The positive predictive value of cardiac CTA is estimated at approximately 82% and the negative predictive value is around 93%.

Dual Source CT scanners, introduced in 2005, allow higher temporal resolution by acquiring a full CT slice in only half a rotation, thus reducing motion blurring at high heart rates and potentially allowing for shorter breath-hold time. This is particularly useful for ill patients who have difficulty holding their breath or who are unable to take heart-rate lowering medication.

The speed advantages of 64-slice MSCT have rapidly established it as the minimum standard for newly installed CT scanners intended for cardiac scanning. Manufacturers are now actively developing 256-slice and true 'volumetric' scanners, primarily for their improved cardiac scanning performance.

The latest MSCT scanners acquire images only at 70-80% of the R-R interval (late diastole). This prospective gating can reduce effective dose from 10-15mSv to as little as 1.2mSv in follow-up patients acquiring at 75% of the R-R interval. Effective doses at a centre with well trained staff doing coronary imaging can average less than the doses for conventional coronary angiography.

Abdominal and pelvic

CT is a sensitive method for diagnosis of abdominal diseases. It is used frequently to determine stage of cancer and to follow progress. It is also a useful test to investigate acute abdominal pain (especially of the lower quadrants, whereas ultrasound is the preferred first line investigation for right upper quadrant pain). Renal stones, appendicitis, pancreatitis, diverticulitis, abdominal aortic aneurysm, and bowel obstruction are conditions that are readily diagnosed and assessed with CT. CT is also the first line for detecting solid organ injury after trauma.

Oral and/or rectal contrast may be used depending on the indications for the scan. A dilute (2% w/v) suspension of barium sulfate is most commonly used. The concentrated barium sulfate preparations used for fluoroscopy e.g. barium enema are too dense and cause severe artifacts on CT. Iodinated contrast agents may be used if barium is contraindicated (for example, suspicion of bowel injury). Other agents may be required to optimize the imaging of specific organs, such as rectally administered gas (air or carbon dioxide) or fluid (water) for a colon study, or oral water for a stomach study.

CT has limited application in the evaluation of the *pelvis*. For the female pelvis in particular, ultrasound and MRI are the imaging modalities of choice. Nevertheless, it may be part of abdominal scanning (e.g. for tumors), and has uses in assessing fractures.

CT is also used in osteoporosis studies and research alongside dual energy X-ray absorptiometry (DXA). Both CT and DXA can be used to assess bone mineral density (BMD) which is used to indicate bone strength, however CT results do not correlate exactly with DXA (the gold standard of BMD measurement). CT is far more expensive, and subjects patients to much higher levels of ionizing radiation, so it is used infrequently.

Extremities

CT is often used to image complex fractures, especially ones around joints, because of its ability to reconstruct the area of interest in multiple planes. Fractures, ligamentous injuries and dislocations can easily be recognised with a 0.2 mm resolution.

Advantages and hazards

Advantages over traditional radiography

There are several advantages that CT has over traditional 2D medical radiography. First, CT completely eliminates the superimposition of images of structures outside the area of interest. Second, because of the inherent high-contrast resolution of CT, differences between tissues that differ in physical density by less than 1% can be distinguished. Finally, data from a single CT imaging procedure consisting of either multiple contiguous or one helical scan can be viewed as images in the axial, coronal, or sagittal planes, depending on the diagnostic task. This is referred to as multiplanar reformatted imaging.

CT is regarded as a moderate to high radiation diagnostic technique. While technical advances have improved radiation efficiency, there has been simultaneous pressure to obtain higher-resolution imaging and use more complex scan techniques, both of which require higher doses of radiation. The improved resolution of CT has permitted the development of new investigations, which may have advantages; compared to conventional angiography for example, CT angiography avoids the invasive insertion of an arterial catheter and guidewire; CT colonography (also known as virtual colonoscopy or VC for short) may be as useful as a barium enema for detection of tumors, but may use a lower radiation dose. CT VC is increasingly being used in the UK as a diagnostic test for bowel cancer and can negate the need for a colonoscopy.

The greatly increased availability of CT, together with its value for an increasing number of conditions, has been responsible for a large rise in popularity. So large has been this rise that, in the most recent comprehensive survey in the United Kingdom, CT scans constituted 7% of all radiologic examinations, but contributed 47% of the total collective dose from medical X-ray examinations in 2000/2001.[6] Increased CT usage has led to an overall rise in the total amount of medical radiation used, despite reductions in other areas. In the United States and Japan for example, there were 26 and 64 CT scanners per 1 million population in 1996. In the U.S., there were about 3 million CT scans performed in 1980, compared to an estimated 62 million scans in 2006.[7]

The radiation dose for a particular study depends on multiple factors: volume scanned, patient build, number and type of scan sequences, and desired resolution and image quality. Additionally, two helical CT scanning parameters that can be adjusted easily and that have a profound effect on radiation dose are tube current and pitch.[8]

The increased use of CT scans has been the greatest in two fields: screening of adults (screening CT of the lung in smokers, virtual colonoscopy, CT cardiac screening and whole-body CT in asymptomatic patients) and CT imaging of children. Shortening of the scanning time to around one second, eliminating the strict need for subject to remain still or be sedated, is one of the main reasons for large increase in the pediatric population (especially for the diagnosis of appendicitis).[7] CT scans of children have been estimated to produce non-negligible increases in the probability of lifetime cancer mortality leading to calls for the use of reduced current settings for CT scans of children.[9] These calculations

are based on the assumption of a linear relationship between radiation dose and cancer risk; this claim is controversial, as some but not all evidence shows that smaller radiation doses are less harmful.[7] Estimated lifetime cancer mortality risks attributable to the radiation exposure from a CT in a 1-year-old are 0.18% (abdominal) and 0.07% (head)—an order of magnitude higher than for adults—although those figures still represent a small increase in cancer mortality over the background rate. In the United States, of approximately 600,000 abdominal and head CT examinations annually performed in children under the age of 15 years, a rough estimate is that 500 of these individuals might ultimately die from cancer attributable to the CT radiation .[10] The additional risk is still very low (0.35%) compared to the background risk of dying from cancer (23%).[10] However, if these statistics are extrapolated to the current number of CT scans, the additional rise in cancer mortality could be 1.5 to 2%. Furthermore, certain conditions can require children to be exposed to multiple CT scans. Again, these calculations can be problematic because the assumptions underlying them could overestimate the risk.[7]

CT scans can be performed with different settings for lower exposure in children, although these techniques are often not employed. Surveys have suggested that currently, many CT scans are performed unnecessarily. Ultrasound scanning or magnetic resonance imaging are alternatives (for example, in appendicitis or brain imaging) without the risk of radiation exposure. Although CT scans come with an additional risk of cancer, especially in children, the benefits that stem from their use outweighs the risk in many cases.[10] Studies support informing parents of the risks of pediatric CT scanning.[11]

Typical scan doses

Examination	Typical effective dose (mSv)	(milli rem)
Chest X-ray	0.1	10
Head CT	1.5[12]	150
Screening mammography	3[7]	300
Abdomen CT	5.3[12]	530
Chest CT	5.8[12]	580
Chest, Abdomen and Pelvis CT	9.9[12]	990
CT colonography (virtual colonoscopy)	3.6 - 8.8	360 - 880
Cardiac CT angiogram	6.7-13[13]	670 - 1300
Barium enema	15[7]	1500
Neonatal abdominal CT	20[7]	2000

For purposes of comparison the average background exposure in the UK is 1-3 mSv per annum.

Adverse reactions to contrast agents

Because contrast CT scans rely on intravenously administered contrast agents in order to provide superior image quality, there is a low but non-negligible level of risk associated with the contrast agents themselves. Many patients report nausea and discomfort, including warmth in the crotch which mimics the sensation of wetting oneself. Certain patients may experience severe and potentially life-threatening allergic reactions to the contrast dye.

The contrast agent may also induce kidney damage. The risk of this is increased with patients who have preexisting renal insufficiency, preexisting diabetes, or reduced intravascular volume. In general, if a patient has normal kidney function, then the risks of contrast nephropathy are negligible. Patients with mild kidney impairment are usually advised to ensure full hydration for several hours before and after the injection. For moderate kidney failure, the use of iodinated contrast should be avoided; this may mean using an alternative technique instead of CT e.g. MRI. Perhaps paradoxically, patients with severe renal failure requiring dialysis do not require special precautions, as their kidneys have so little function remaining that any further damage would not be noticeable and the dialysis will remove the contrast agent.

Low-Dose CT Scan

The main issue within radiology today is how to reduce the radiation dose during CT examinations without compromising the image quality. Generally, a high radiation dose results in high-quality images. A lower dose leads to increased image noise and results in unsharp images. Unfortunately, as the radiation dose increases, so does the associated risk of radiation induced cancer - even though this is extremely small. A radiation exposure of around 1200 mrem (similar to a 4-view mammogram) carried a radiation-induced cancer risk of about a million to one. However, there are several methods that can be used in order to lower the exposure to ionizing radiation during a CT scan.

1. New software technology can significantly reduce the radiation dose. The software works as a filter that reduces random noise and enhances structures. In this way, it is possible to get high-quality images and at the same time lower the dose by as much as 30 to 70 percent.
2. Individualize the examination and adjust the radiation dose to the body type and body organ examined. Different body types and organs require different amounts of radiation.
3. Prior to every CT examination, evaluate the appropriateness of the exam whether it is motivated or if another type of examination is more suitable.

Computed Tomography versus MRI

See the entries or paragraphs of the same name in the MRI and 2D-FT NMRI and Spectroscopy articles. The basic mathematics of the 2D-Fourier transform in CT reconstruction is very similar to the 2D-FT NMRI, but the computer data processing in CT does differ in detail, as for example in the case of the volume rendering or the artifacts elimination algorithms that are specific to CT.

Process

X-ray slice data is generated using an X-ray source that rotates around the object; X-ray sensors are positioned on the opposite side of the circle from the X-ray source. The earliest sensors were scintillation detectors, with photomultiplier tubes excited by (typically) cesium iodide crystals. Cesium iodide was replaced during the eighties by ion chambers containing high pressure Xenon gas. These systems were in turn replaced by scintillation systems based on photo diodes instead of photomultipliers and modern scintillation materials with more desirable characteristics. Many data scans are progressively taken as the object is gradually passed through the gantry. They are combined together by the mathematical procedures known as tomographic

CT scan illustration

reconstruction. The data are arranged in a matrix in memory, and each data point is convolved with its neighbours according with a seed algorithm using Fast Fourier Transform techniques. This dramatically increases the resolution of each Voxel (volume element). Then a process known as Back Projection essentially reverses the acquisition geometry and stores the result in another memory array. This data can then be displayed, photographed, or used as input for further processing, such as multi-planar reconstruction.

Newer machines with faster computer systems and newer software strategies can process not only individual cross sections but continuously changing cross sections as the gantry, with the object to be imaged, is slowly and smoothly slid through the X-ray circle. These are called *helical* or *spiral CT* machines. Their computer systems integrate the data of the moving individual slices to generate three dimensional volumetric information (3D-CT scan), in turn viewable from multiple different perspectives on attached CT workstation monitors. This type of data acquisition requires enormous processing power, as the data are arriving in a continuous stream and must be processed in real-time.

In conventional CT machines, an X-ray tube and detector are physically rotated behind a circular shroud (see the image above right); in the electron beam tomography (EBT) the tube is far larger and higher power to support the high temporal resolution. The electron beam is deflected in a hollow funnel shaped vacuum chamber. X-rays are generated when the beam hits the stationary target. The detector is also stationary. This arrangement can result in very fast scans, but is extremely expensive.

The data stream representing the varying radiographic intensity sensed at the detectors on the opposite side of the circle during each sweep is then computer processed to calculate cross-sectional estimations of the radiographic density, expressed in Hounsfield units. Sweeps cover 360 or just over 180 degrees in conventional machines, 220 degrees in EBT.
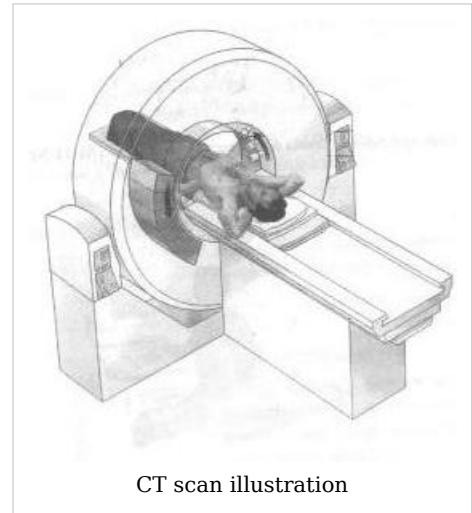
CT is used in medicine as a diagnostic tool and as a guide for interventional procedures. Sometimes contrast materials such as intravenous iodinated contrast are used. This is useful to highlight structures such as blood vessels that otherwise would be difficult to delineate from their surroundings. Using contrast material can also help to obtain functional information about tissues.

Pixels in an image obtained by CT scanning are displayed in terms of relative radiodensity. The pixel itself is displayed according to the mean attenuation of the tissue(s) that it corresponds to on a scale from +3071 (most attenuating) to -1024 (least attenuating) on the Hounsfield scale. Pixel is a two dimensional unit

CT scanner with cover removed to show the principle of operation

based on the matrix size and the field of view. When the CT slice thickness is also factored in, the unit is known as a Voxel, which is a three dimensional unit. The phenomenon that one part of the detector cannot differentiate between different tissues is called the "*Partial Volume Effect*". That means that a big amount of cartilage and a thin layer of compact bone can cause the same attenuation in a voxel as hyperdense cartilage alone. Water has an attenuation of 0 Hounsfield units (HU) while air is -1000 HU, cancellous bone is typically +400 HU, cranial bone can reach 2000 HU or more (os temporale) and can cause artifacts. The attenuation of metallic implants depends on atomic number of the element used: Titanium usually has an amount of +1000 HU, iron steel can completely extinguish the X-ray and is therefore responsible for well-known line-artifacts in computed tomograms. Artifacts are caused by abrupt transitions between low- and high-density materials, which results in data values that exceed the dynamic range of the processing electronics.

Windowing

Windowing is the process of using the calculated Hounsfield units to make an image. A typical display device can only resolve 256 shades of gray, some specialty medical displays can resolve up to 1024 shades of gray. These shades of gray can be distributed over a wide range of HU values to get an overview of structures that attenuate the beam to widely varying degrees. Alternatively, these shades of gray can be distributed over a narrow range of HU values (called a "*narrow window*") centered over the average HU value of a particular structure to be evaluated. In this way, subtle variations in the internal makeup of the structure can be discerned. This is a commonly used image processing technique known as contrast compression. For example, to evaluate the abdomen in order to find subtle masses in the liver, one might use liver windows. Choosing 70 HU as an average HU value for liver, the shades of gray can be distributed over a narrow window or range. One could use 170 HU as the narrow window, with 85 HU above the 70 HU average value; 85 HU below it. Therefore the liver window would extend from -15 HU to +155 HU. All the shades of gray for the image would be distributed in this range of Hounsfield values. Any HU value below -15 would be pure black, and any HU value above 155 HU would be pure white in this example. Using this same logic, bone windows would use a "*wide window*" (to evaluate everything from fat-containing medullary bone that contains the marrow, to the dense cortical bone), and the center or level would be a value in the hundreds of Hounsfield units.

To an untrained person, these window controls would correspond to the more familiar "Brightness" (Window Level) and "Contrast" (Window Width).

Artifacts

Although CT is a relatively accurate test, it is liable to produce artifacts, such as the following.

- **Aliasing Artifact or Streaks**

These appear as dark lines which radiate away from sharp corners. It occurs because it is impossible for the scanner to 'sample' or take enough projections of the object, which is usually metallic. It can also occur when an insufficient X-ray tube current is selected, and insufficient penetration of the x-ray occurs. These artifacts are also closely tied to motion during a scan.

CT number profile   Image of uniform phantom

Example of Beam Hardening

This type of artifact commonly occurs in head images around the pituitary fossa area.

- **Partial Volume Effect**

This appears as 'blurring' over sharp edges. It is due to the scanner being unable to differentiate between a small amount of high-density material (e.g. bone) and a larger amount of lower density (e.g. cartilage). The processor tries to average out the two densities or structures, and information is lost. This can be partially overcome by scanning using thinner slices.

- **Ring Artifact**

Probably the most common mechanical artifact, the image of one or many 'rings' appears within an image. This is usually due to a detector fault.

- **Noise Artifact**

This appears as graining on the image and is caused by a low signal to noise ratio. This occurs more commonly when a thin slice thickness is used. It can also occur when the power supplied to the X-ray tube is insufficient to penetrate the anatomy.

- **Motion Artifact**

This is seen as blurring and/or streaking which is caused by movement of the object being imaged.

- **Windmill**

Streaking appearances can occur when the detectors intersect the reconstruction plane. This can be reduced with filters or a reduction in pitch.

- **Beam Hardening**

This can give a 'cupped appearance'. It occurs when there is more attenuation in the center of the object than around the edge. This is easily corrected by filtration and software.
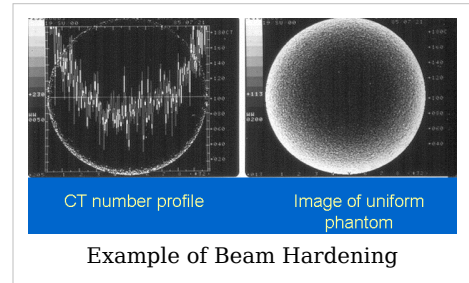
Three-dimensional (3D) image reconstruction

The principle

Because contemporary CT scanners offer isotropic, or near isotropic, resolution, display of images does not need to be restricted to the conventional axial images. Instead, it is possible for a software program to build a volume by 'stacking' the individual slices one on top of the other. The program may then display the volume in an alternative manner.

Multiplanar reconstruction

Multiplanar reconstruction (MPR) is the simplest method of reconstruction. A volume is built by stacking the axial slices. The software then cuts slices through the volume in a different plane (usually orthogonal). Optionally, a special projection method, such as maximum-intensity projection (MIP) or minimum-intensity projection (mIP), can be used to build the reconstructed slices.

MPR is frequently used for examining the spine. Axial images through the spine will only show one vertebral body at a time and cannot reliably show the intervertebral discs. By reformatting the volume, it becomes much easier to visualise the position of one vertebral body in relation to the others.

Typical screen layout for diagnostic software, showing one 3D and three MPR views

Modern software allows reconstruction in non-orthogonal (oblique) planes so that the optimal plane can be chosen to display an anatomical structure. This may be particularly useful for visualising the structure of the bronchi as these do not lie orthogonal to the direction of the scan.

For vascular imaging, curved-plane reconstruction can be performed. This allows bends in a vessel to be 'straightened' so that the entire length can be visualised on one image, or a short series of images. Once a vessel has been 'straightened' in this way, quantitative measurements of length and cross sectional area can be made, so that surgery or interventional treatment can be planned.

MIP reconstructions enhance areas of high radiodensity, and so are useful for angiographic studies. mIP reconstructions tend to enhance air spaces so are useful for assessing lung structure.

3D rendering techniques

Surface rendering

A threshold value of radiodensity is chosen by the operator (e.g. a level that corresponds to bone). A threshold level is set, using edge detection image processing algorithms. From this, a 3-dimensional model can be constructed and displayed on screen. Multiple models can be constructed from various different thresholds, allowing different colors to represent each anatomical component such as bone, muscle, and cartilage. However, the interior structure of each element is not visible in this mode of operation.

Volume rendering

Surface rendering is limited in that it will only display surfaces which meet a threshold density, and will only display the surface that is closest to the imaginary viewer. In volume rendering, transparency and colors are used to allow a better representation of the volume to be shown in a single image - e.g. the bones of the pelvis could be displayed as semi-transparent, so that even at an oblique angle, one part of the image does not conceal another.

Image segmentation

Where different structures have similar radiodensity, it can become impossible to separate them simply by adjusting volume rendering parameters. The solution is called segmentation, a manual or automatic procedure that can remove the unwanted structures from the image.

Example

Some slices of a cranial CT scan are shown below. The bones are whiter than the surrounding area. (Whiter means higher attenuation.) Note the blood vessels (arrowed) showing brightly due to the injection of an iodine-based contrast agent.
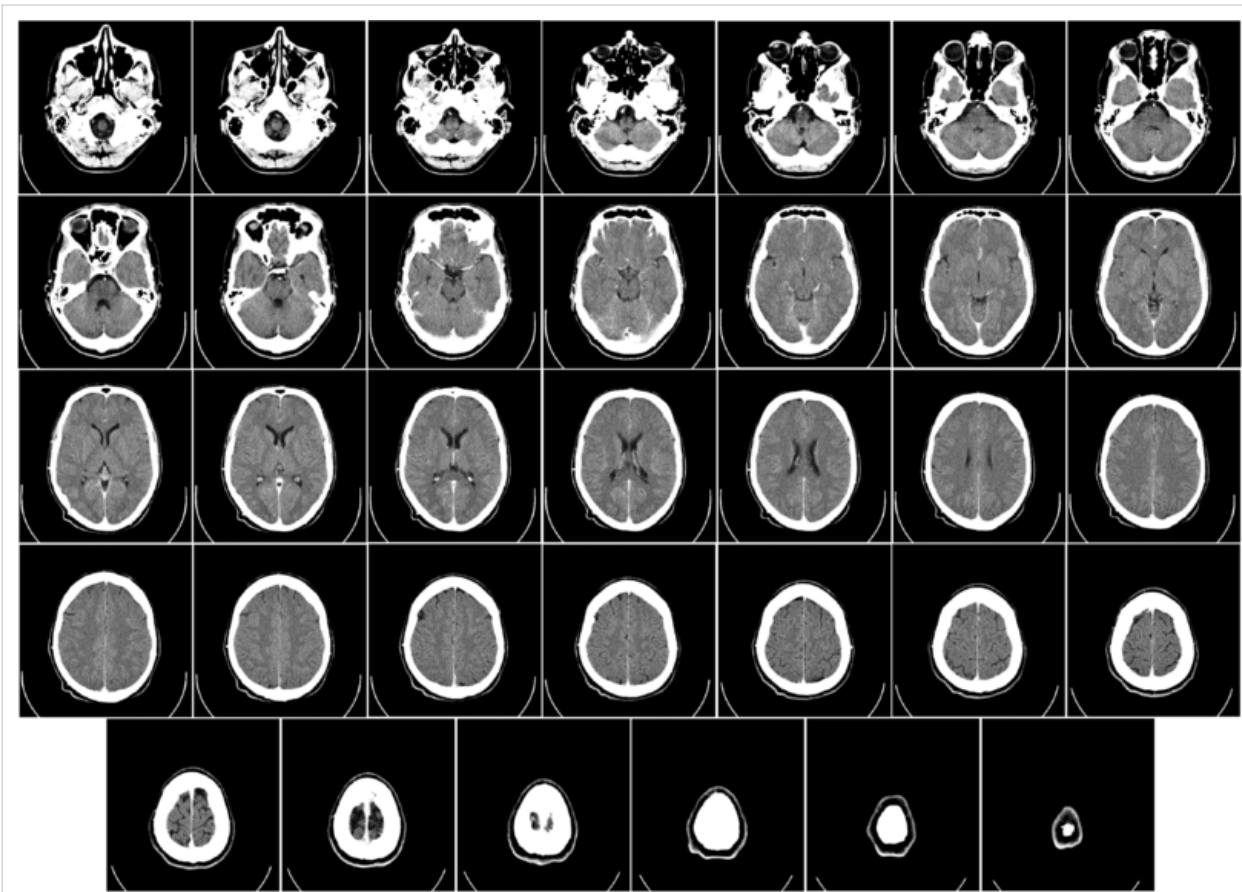
Computed tomography of human brain, from base of the skull to top. Taken with intravenous contrast medium.

A volume rendering of this volume clearly shows the high density bones.

Bone reconstructed in 3D
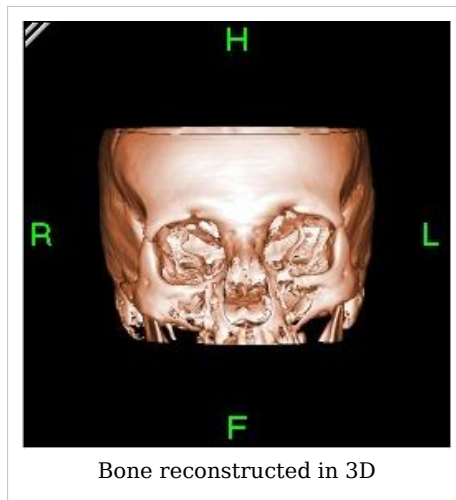
After using a segmentation tool to remove the bone, the previously concealed vessels can now be demonstrated.

Brain vessels reconstructed in 3D after bone has been removed by segmentation
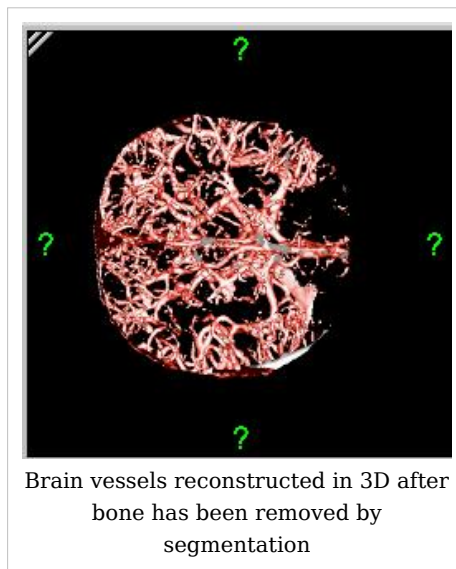
See also

- Xenon-enhanced CT scanning

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External links

- Open-source computed tomography simulator with educational tracing displays (http://ctsim.org)
- idoimaging.com: Free software for viewing CT and other medical imaging files (http://www.idoimaging.com)
- CT Artefacts (http://www.impactscan.org/slides/impactcourse/artefacts/img0.html) by David Platten
- DigiMorph (http://digimorph.org/) A library of 3D imagery based on CT scans of the internal and external structure of living and extinct plants and animals.
- MicroCT and calcified tissues (http://www.med.univ-angers.fr/discipline/lab_histo/page_microCT.htm) A website dedicated to microCT in the microscopic analysis of calcified tissues.
- Free Radiology Resource for Radiologists, Radiographers, and Technical Assistance (http://www.mdct.com.au:)
- Radiation Risk Calculator (http://www.xrayrisk.com) Calculate cancer risk from CT scans and xrays.

Chemical imaging

Chemical imaging is the simultaneous measurement of spectra (chemical information) and images or pictures (spatial information)[1] [2] The technique is most often applied to either solid or gel samples, and has applications in chemistry, biology[3] [4] [5] [6] [7] [8] , medicine[9] [10] , pharmacy[11] (see also for example: Chemical Imaging Without Dyeing [12]), food science, biotechnology[13] [14] , agriculture and industry (see for example:NIR Chemical Imaging in Pharmaceutical Industry [15] and Pharmaceutical Process Analytical Technology: [16]). NIR, IR and Raman chemical imaging is also referred to as hyperspectral, spectroscopic, spectral or multispectral imaging (also see microspectroscopy). However, other ultra-sensitive and selective, chemical imaging techniques are also in use that involve either UV-visible or fluorescence microspectroscopy. Chemical imaging techniques can be used to analyze samples of all sizes, from the single molecule[17] [18] to the cellular level in biology and medicine[19] [20] [21] , and to images of planetary systems in astronomy, but different instrumentation is employed for making observations on such widely different systems.

Chemical imaging instrumentation is composed of three components: a radiation source to illuminate the sample, a spectrally selective element, and usually a detector array (the camera) to collect the images. When many stacked spectral channels (wavelengths) are collected for different locations of the microspectrometer focus on a line or planar array in the focal plane, the data is called hyperspectral; fewer wavelength data sets are called multispectral. The data format is called a hypercube. The data set may be visualized as a three-dimensional block of data spanning two spatial dimensions (x and y), with a series of wavelengths (lambda) making up the third (spectral) axis. The hypercube can be visually and mathematically treated as a series of spectrally resolved images (each image plane corresponding to the image at one wavelength) or a series of spatially resolved spectra. The analyst may choose to view the spectrum measured at a particular spatial location; this is useful for chemical identification. Alternatively, selecting an image plane at a particular wavelength can highlight the spatial distribution of sample components, provided that their spectral signatures are different at the selected wavelength.

Many materials, both manufactured and naturally occurring, derive their functionality from the spatial distribution of sample components. For example, extended release pharmaceutical formulations can be achieved by using a coating that acts as a barrier layer. The release of active ingredient is controlled by the presence of this barrier, and imperfections in the coating, such as discontinuities, may result in altered performance. In the semi-conductor industry, irregularities or contaminants in silicon wafers or printed micro-circuits can lead to failure of these components. The functionality of biological systems is also dependent upon chemical gradients – a single cell, tissue, and even whole organs function because of the very specific arrangement of components. It has been shown that even small changes in chemical composition and distribution may be an early indicator of disease.

Any material that depends on chemical gradients for functionality may be amenable to study by an analytical technique that couples spatial and chemical characterization. To efficiently and effectively design and manufacture such materials, the 'what' and the 'where' must both be measured. The demand for this type of analysis is increasing as manufactured materials become more complex. Chemical imaging techniques not only

permit visualization of the spatially resolved chemical information that is critical to understanding modern manufactured products, but it is also a non-destructive technique so that samples are preserved for further testing.

History

Commercially available laboratory-based chemical imaging systems emerged in the early 1990s (ref. 1-5). In addition to economic factors, such as the need for sophisticated electronics and extremely high-end computers, a significant barrier to commercialization of infrared imaging was that the focal plane array (FPA) needed to read IR images were not readily available as commercial items. As high-speed electronics and sophisticated computers became more commonplace, and infrared cameras became readily commercially available, laboratory chemical imaging systems were introduced.

Initially used for novel research in specialized laboratories, chemical imaging became a more commonplace analytical technique used for general R&D, quality assurance (QA) and quality control (QC) in less than a decade. The rapid acceptance of the technology in a variety of industries (pharmaceutical, polymers, semiconductors, security, forensics and agriculture) rests in the wealth of information characterizing both chemical composition and morphology. The parallel nature of chemical imaging data makes it possible to analyze multiple samples simultaneously for applications that require high throughput analysis in addition to characterizing a single sample.

Principles

Chemical imaging shares the fundamentals of vibrational spectroscopic techniques, but provides additional information by way of the simultaneous acquisition of spatially resolved spectra. It combines the advantages of digital imaging with the attributes of spectroscopic measurements. Briefly, vibrational spectroscopy measures the interaction of light with matter. Photons that interact with a sample are either absorbed or scattered; photons of specific energy are absorbed, and the pattern of absorption provides information, or a fingerprint, on the molecules that are present in the sample.

On the other hand, in terms of the observation setup, chemical imaging can be carried out in one of the following modes: (optical) absorption, emission (fluorescence), (optical) transmission or scattering (Raman). A consensus currently exists that the fluorescence (emission) and Raman scattering modes are the most sensitive and powerful, but also the most expensive.

In a transmission measurement, the radiation goes through a sample and is measured by a detector placed on the far side of the sample. The energy transferred from the incoming radiation to the molecule(s) can be calculated as the difference between the quantity of photons that were emitted by the source and the quantity that is measured by the detector. In a diffuse reflectance measurement, the same energy difference measurement is made, but the source and detector are located on the same side of the sample, and the photons that are measured have re-emerged from the illuminated side of the sample rather than passed through it. The energy may be measured at one or multiple wavelengths; when a series of measurements are made, the response curve is called a spectrum.

A key element in acquiring spectra is that the radiation must somehow be energy selected – either before or after interacting with the sample. Wavelength selection can be

accomplished with a fixed filter, tunable filter, spectrograph, an interferometer, or other devices. For a fixed filter approach, it is not efficient to collect a significant number of wavelengths, and multispectral data are usually collected. Interferometer-based chemical imaging requires that entire spectral ranges be collected, and therefore results in hyperspectral data. Tunable filters have the flexibility to provide either multi- or hyperspectral data, depending on analytical requirements.

Spectra may be measured one point at a time using a single element detector (single-point mapping), as a line-image using a linear array detector (typically 16 to 28 pixels) (linear array mapping), or as a two-dimensional image using a Focal Plane Array (FPA)(typically 256 to 16,384 pixels) (FPA imaging). For single-point the sample is moved in the x and y directions point-by-point using a computer-controlled stage. With linear array mapping, the sample is moved line-by-line with a computer-controlled stage. FPA imaging data are collected with a two-dimensional FPA detector, hence capturing the full desired field-of-view at one time for each individual wavelength, without having to move the sample. FPA imaging, with its ability to collected tens of thousands of spectra simultaneously is orders of magnitude faster than linear arrays which are can typically collect 16 to 28 spectra simultaneously, which are in turn much faster than single-point mapping.

Terminology

Some words common in spectroscopy, optical microscopy and photography have been adapted or their scope modified for their use in chemical imaging. They include: resolution, field of view and magnification. There are two types of resolution in chemical imaging. The spectral resolution refers to the ability to resolve small energy differences; it applies to the spectral axis. The spatial resolution is the minimum distance between two objects that is required for them to be detected as distinct objects. The spatial resolution is influenced by the field of view, a physical measure of the size of the area probed by the analysis. In imaging, the field of view is a product of the magnification and the number of pixels in the detector array. The magnification is a ratio of the physical area of the detector array divided by the area of the sample field of view. Higher magnifications for the same detector image a smaller area of the sample.

Types of vibrational chemical imaging instruments

Chemical imaging has been implemented for mid-infrared, near-infrared spectroscopy and Raman spectroscopy. As with their bulk spectroscopy counterparts, each imaging technique has particular strengths and weaknesses, and are best suited to fulfill different needs.

Mid-infrared chemical imaging

Mid-infrared (MIR) spectroscopy probes fundamental molecular vibrations, which arise in the spectral range 2,500-25,000 nm. Commercial imaging implementations in the MIR region typically employ Fourier Transform Infrared (FT-IR) interferometers and the range is more commonly presented in wavenumber, 4,000 – 400 cm^{-1}. The MIR absorption bands tend to be relatively narrow and well-resolved; direct spectral interpretation is often possible by an experienced spectroscopist. MIR spectroscopy can distinguish subtle changes in chemistry and structure, and is often used for the identification of unknown materials. The absorptions in this spectral range are relatively strong; for this reason, sample presentation is important to limit the amount of material interacting with the

incoming radiation in the MIR region. Most data collected in this range is collected in transmission mode through thin sections (~10 micrometres) of material. Water is a very strong absorber of MIR radiation and wet samples often require advanced sampling procedures (such as attenuated total reflectance). Commercial instruments include point and line mapping, and imaging. All employ an FT-IR interferometer as wavelength selective element and light source.

For types of MIR microscope, see Microscopy#infrared microscopy.

Atmospheric windows in the infrared spectrum are also employed to perform chemical imaging remotely. In these spectral regions the atmospheric gases (mainly water and CO_2) present low absorption and allow infrared viewing over kilometer
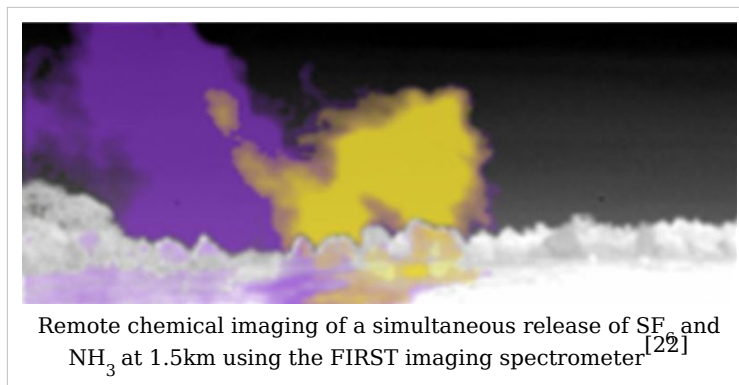
Remote chemical imaging of a simultaneous release of SF_6 and NH_3 at 1.5km using the FIRST imaging spectrometer[22]

distances. Target molecules can then be viewed using the selective absorption/emission processes described above. An example of the chemical imaging of a simultaneous release of SF_6 and NH_3 is shown in the image.

Near-infrared chemical imaging

The analytical near infrared (NIR) region spans the range from approximately 700-2,500 nm. The absorption bands seen in this spectral range arise from overtones and combination bands of O-H, N-H, C-H and S-H stretching and bending vibrations. Absorption is one to two orders of magnitude smaller in the NIR compared to the MIR; this phenomenon eliminates the need for extensive sample preparation. Thick and thin samples can be analyzed without any sample preparation, it is possible to acquire NIR chemical images through some packaging materials, and the technique can be used to examine hydrated samples, within limits. Intact samples can be imaged in transmittance or diffuse reflectance.

The lineshapes for overtone and combination bands tend to be much broader and more overlapped than for the fundamental bands seen in the MIR. Often, multivariate methods are used to separate spectral signatures of sample components. NIR chemical imaging is particularly useful for performing rapid, reproducible and non-destructive analyses of known materials[23] [24] . NIR imaging instruments are typically based on one of two platforms: imaging using a tunable filter and broad band illumination, and line mapping employing an FT-IR interferometer as the wavelength filter and light source.

Raman chemical imaging

The Raman shift chemical imaging spectral range spans from approximately 50 to 4,000 cm^{-1}; the actual spectral range over which a particular Raman measurement is made is a function of the laser excitation frequency. The basic principle behind Raman spectroscopy differs from the MIR and NIR in that the x-axis of the Raman spectrum is measured as a function of energy shift (in cm^{-1}) relative to the frequency of the laser used as the source of radiation. Briefly, the Raman spectrum arises from inelastic scattering of incident photons, which requires a change in polarizability with vibration, as opposed to infrared absorption, which requires a change in dipole moment with vibration. The end result is spectral

information that is similar and in many cases complementary to the MIR. The Raman effect is weak - only about one in 10^7 photons incident to the sample undergoes Raman scattering. Both organic and inorganic materials possess a Raman spectrum; they generally produce sharp bands that are chemically specific. Fluorescence is a competing phenomenon and, depending on the sample, can overwhelm the Raman signal, for both bulk spectroscopy and imaging implementations.

Raman chemical imaging requires little or no sample preparation. However, physical sample sectioning may be used to expose the surface of interest, with care taken to obtain a surface that is as flat as possible. The conditions required for a particular measurement dictate the level of invasiveness of the technique, and samples that are sensitive to high power laser radiation may be damaged during analysis. It is relatively insensitive to the presence of water in the sample and is therefore useful for imaging samples that contain water such as biological material.

Fluorescence imaging (visible and NIR)

This emission microspectroscopy mode is the most sensitive in both visible and FT-NIR microspectroscopy, and has therefore numerous biomedical, biotechnological and agricultural applications. There are several powerful, highly specific and sensitive fluorescence techniques that are currently in use, or still being developed; among the former are FLIM, FRAP, FRET and FLIM-FRET; among the latter are NIR fluorescence and probe-sensitivity enhanced NIR fluorescence microspectroscopy and nanospectroscopy techniques (see "Further reading" section).

Sampling and samples

The value of imaging lies in the ability to resolve spatial heterogeneities in solid-state or gel/gel-like samples. Imaging a liquid or even a suspension has limited use as constant sample motion serves to average spatial information, unless ultra-fast recording techniques are employed as in fluorescence correlation microspectroscopy or FLIM obsevations where a single molecule may be monitored at extremely high (photon) detection speed. High-throughput experiments (such as imaging multi-well plates) of liquid samples can however provide valuable information. In this case, the parallel acquisition of thousands of spectra can be used to compare differences between samples, rather than the more common implementation of exploring spatial heterogeneity within a single sample.

Similarly, there is no benefit in imaging a truly homogeneous sample, as a single point spectrometer will generate the same spectral information. Of course the definition of homogeneity is dependent on the spatial resolution of the imaging system employed. For MIR imaging, where wavelengths span from 3-10 micrometres, objects on the order of 5 micrometres may theoretically be resolved. The sampled areas are limited by current experimental implementations because illumination is provided by the interferometer. Raman imaging may be able to resolve particles less than 1 micrometre in size, but the sample area that can be illuminated is severely limited. With Raman imaging, it is considered impractical to image large areas and, consequently, large samples. FT-NIR chemical/hyperspectral imaging usually resolves only larger objects (>10 micrometres), and is better suited for large samples because illumination sources are readily available. However, FT-NIR microspectroscopy was recently reported to be capable of about 1.2 micron (micrometer) resolution in biological samples[25] Furthermore, two-photon

excitation FCS experiments were reported to have attained 15 nanometer resolution on biomembrane thin films with a special coincidence photon-counting setup.

Detection limit

The concept of the detection limit for chemical imaging is quite different than for bulk spectroscopy, as it depends on the sample itself. Because a bulk spectrum represents an average of the materials present, the spectral signatures of trace components are simply overwhelmed by dilution. In imaging however, each pixel has a corresponding spectrum. If the physical size of the trace contaminant is on the order of the pixel size imaged on the sample, its spectral signature will likely be detectable. If however, the trace component is dispersed homogeneously (relative to pixel image size) throughout a sample, it will not be detectable. Therefore, detection limits of chemical imaging techniques are strongly influenced by particle size, the chemical and spatial heterogeneity of the sample, and the spatial resolution of the image.

Data analysis

Data analysis methods for chemical imaging data sets typically employ mathematical algorithms common to single point spectroscopy or to image analysis. The reasoning is that the spectrum acquired by each detector is equivalent to a single point spectrum; therefore pre-processing, chemometrics and pattern recognition techniques are utilized with the similar goal to separate chemical and physical effects and perform a qualitative or quantitative characterization of individual sample components. In the spatial dimension, each chemical image is equivalent to a digital image and standard image analysis and robust statistical analysis can be used for feature extraction.

See also

- Multispectral image
- Microspectroscopy
- Imaging spectroscopy

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- NIR Chemical Imaging for Counterfeit Pharmaceutical Product Analysis (http://www. spectroscopymag.com/spectroscopy/Near-IR+Spectroscopy/ NIR-Chemical-Imaging-for-Counterfeit-Pharmaceutica/ArticleStandard/Article/detail/ 406629)
- Chemical Imaging: Potential New Crime Busting Tool (http://www.sciencedaily.com/ releases/2007/08/070802103435.htm)
- Chemical Imaging Without Dyeing (http://witec.de/en/download/Raman/ ImagingMicroscopy04.pdf) - Chemical Imaging Without Dyeing

Hyperspectral imaging

Hyperspectral imaging collects and processes information from across the electromagnetic spectrum. Unlike the human eye, which just sees visible light, hyperspectral imaging is more like the eyes of the mantis shrimp, which can see visible light as well as from the ultraviolet to infrared. Hyperspectral capabilities enable the mantis shrimp to recognize different types of coral, prey, or predators, all which may appear as the same color to the human eye.

Humans build sensors and processing systems to provide the same type of capability for application in agriculture, mineralogy, physics, and surveillance. Hyperspectral sensors look at objects using a vast portion of the electromagnetic spectrum. Certain objects leave unique 'fingerprints' across the electromagnetic spectrum. These 'fingerprints' are known as spectral signatures and enable identification of the materials that make up a scanned object. For example, having the spectral signature for oil helps mineralogists find new oil fields.

Acquisition and Analysis
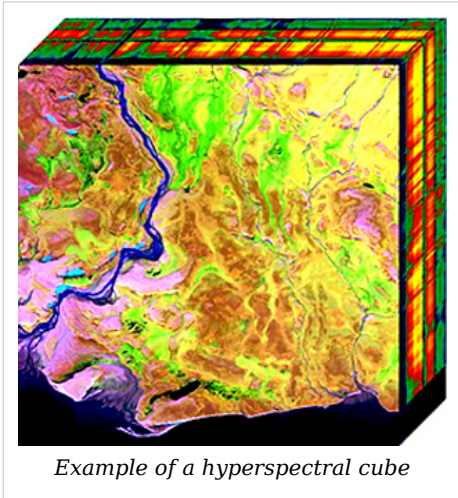
Example of a hyperspectral cube

Hyperspectral sensors collect information as a set of 'images'. Each image represents a range of the electromagnetic spectrum and is also known as a spectral band. These 'images' are then combined and form a three dimensional hyperspectral cube for processing and analysis.

Hyperspectral cubes are generated from airborne sensors like the NASA's *Airborne Visible/Infrared Imaging Spectrometer* (AVIRIS), or from satellites like NASA's Hyperion.[1] However, for many development and validation studies handheld sensors are used.[2]

The precision of these sensors is typically measured in spectral resolution, which is the width of each band of the spectrum that is captured. If the scanner picks up on a large number of fairly narrow frequency bands, it is possible to identify objects even if said objects are only captured in a handful of pixels. However, spatial resolution is a factor in addition to spectral resolution. If the pixels are too large, then multiple objects are captured in the same pixel and become difficult to identify. If the pixels are too small, then the energy captured by each sensor-cell is low, and the decreased signal-to-noise ratio reduces the reliability of measured features.

MicroMSI, Opticks and Envi are three remote sensing applications that support the processing and analysis of hyperspectral data. The acquisition and processing of hyperspectral images is also referred to as imaging spectroscopy.

Differences between Hyperspectral and Multispectral

Hyperspectral Imaging is part of a class of techniques commonly referred to as spectral imaging or spectral analysis. Hyperspectral Imaging is related to multispectral imaging. The distinction between hyperspectral and multispectral is usually defined as the number of spectral bands. Multispectral data contains from tens to hundreds of bands. Hyperspectral data contains hundreds to thousands of bands. However, hyperspectral imaging may be best defined by the manner in which the data is collected. Hyperspectral data is a set of contiguous bands (usually by one sensor). Multispectral is a set of optimally chosen spectral bands that are typically not contiguous and can be collected from multiple sensors.
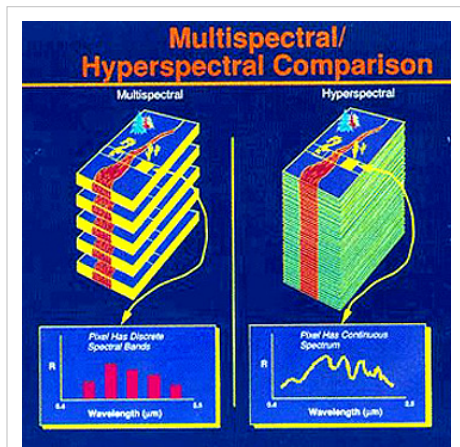
Hyperspectral and Multispectral Differences.

Applications

Hyperspectral remote sensing is used in a wide array of real-life applications. Although originally developed for mining and geology (The ability of hyperspectral imaging to identify various minerals makes it ideal for the mining and oil industries, where it can be used to look for ore and oil[2] [3] it has now spread into fields as wide-spread as ecology and surveillance, as well as historical manuscript research such as the imaging of the Archimedes Palimpsest. This technology is continually becoming more available to the public, and has been used in a wide variety of ways. Organizations such as NASA and the USGS have catalogues of various minerals and their spectral signatures, and have posted them online to make them readily available for researchers.

Agriculture

Although the costs of acquiring hyperspectral images is typically high, for specific crops and in specific climates hyperspectral remote sensing is used more and more for monitoring the development and health of crops. In Australia work is underway to use imaging spectrometers to detect grape variety, and develop an early warning system for disease outbreaks.[4] Furthermore work is underway to use hyperspectral data to detect the chemical composition of plants[5] which can be used to detect the nutrient and water status of wheat in irrigated systems[6]

Mineralogy

The original field of development for hyperspectral remote sensing, hyperspectral sensing of minerals is now well developed. Many minerals can be identified from images, and their relation to the presence of valuable minerals such as gold and diamonds is well understood. Currently the move is towards understanding the relation between oil and gas leakages from pipelines and natural wells; their effect on the vegetation and the spectral signatures. Recent work includes the PhD dissertations of Werff[7] and Noomen[8] .

Physics

Physicists use an electron microscopy technique that involves microanalysis using either Energy dispersive X-ray spectroscopy (EDS), Electron energy loss spectroscopy (EELS), Infrared Spectroscopy(IR), Raman Spectroscopy, or cathodoluminescence (CL) spectroscopy, in which the entire spectrum measured at each point is recorded. EELS hyperspectral imaging is performed in a scanning transmission electron microscope (STEM); EDS and CL mapping can be performed in STEM as well, or in a scanning electron microscope or electron probe microanalyzer (EPMA). Often, multiple techniques (EDS, EELS, CL) are used simultaneously.

In a "normal" mapping experiment, an image of the sample will be made that is simply the intensity of a particular emission mapped in an XY raster. For example, an EDS map could be made of a steel sample, in which iron x-ray intensity is used for the intensity grayscale of the image. Dark areas in the image would indicate not-iron-bearing impurities. This could potentially give misleading results; if the steel contained tungsten inclusions, for example, the high atomic number of tungsten could result in bremsstrahlung radiation that made the iron-free areas *appear* to be rich in iron.

By hyperspectral mapping, instead, the entire spectrum at each mapping point is acquired, and a quantitative analysis can be performed by computer post-processing of the data, and

a quantitative map of iron content produced. This would show which areas contained no iron, despite the anomalous x-ray counts caused by bremsstrahlung. Because EELS core-loss edges are small signals on top of a large background, hyperspectral imaging allows large improvements to the quality of EELS chemical maps.

Similarly, in CL mapping, small shifts in the peak emission energy could be mapped, which would give information regarding slight chemical composition changes or changes in the stress state of a sample.

Surveillance

Hyperspectral surveillance is the implementation of hyperspectral scanning technology for surveillance purposes. Hyperspectral imaging is particularly useful in military surveillance because of measures that military entities now take to avoid airborne surveillance. Airborne surveillance has been in effect since soldiers used tethered balloons to spy on troops during the American Civil War, and since that time we have learned not only to hide from the naked eye, but to mask our heat signature to blend in to the surroundings and avoid infrared scanning, as well. The idea that drives hyperspectral surveillance is that hyperspectral scanning draws information from such a large portion of the light spectrum that any given object should have unique spectral signature in at least a few of the many bands that get scanned.[1]

Advantages and Disadvantages

The primary advantages to hyperspectral imaging is that, because an entire spectrum is acquired at each point, the operator needs no a priori knowledge of the sample, and post-processing allows all available information from the dataset to be mined.

The primary disadvantages are cost and complexity. Fast computers, sensitive detectors, and large data storage capacities are needed for analyzing hyperspectral data. Significant data storage capacity is necessary since hyperspectral cubes are large multi-dimensional datasets, potentially exceeding hundreds of megabytes. All of these factors greatly increase the cost of acquiring and processing hyperspectral data. Also, one of the hurdles that researchers have had to face is finding ways to program hyperspectral satellites to sort through data on their own and transmit only the most important images, as both transmission and storage of that much data could prove difficult and costly.[1] As a relatively new analytical technique, the full potential of hyperspectral imaging has not yet been realized.

See also

- Airborne Real-time Cueing Hyperspectral Enhanced Reconnaissance
- Full Spectral Imaging
- Multi-spectral image
- Chemical imaging
- Remote Sensing
- Sensor fusion

External Links

ITT Visual Information Solutions - ENVI Hyperspectral Image Processing Software [9]

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Multispectral imaging

1. Redirect Multi-spectral image

Electron Microscopy

1. redirect electron microscope

This is a subject of study.

Rory sees this as a potential money-maker in his bid for pron domination.

Atomic force microscope

The **atomic force microscope** (AFM) or scanning force microscope (SFM) is a very high-resolution type of scanning probe microscopy, with demonstrated resolution of fractions of a nanometer, more than 1000 times better than the optical diffraction limit. The precursor to the AFM, the scanning tunneling microscope, was developed by Gerd Binnig and Heinrich Rohrer in the early 1980s, a development that earned them the Nobel Prize for Physics in 1986. Binnig, Quate and Gerber invented the first AFM in 1986. The AFM is one of the foremost tools for imaging, measuring and manipulating matter at the nanoscale. The information is gathered by "feeling" the surface with a mechanical probe. Piezoelectric elements that facilitate tiny but accurate and precise movements on (electronic) command enable the very precise scanning.

Topographic scan of a glass surface

Microscope AFM
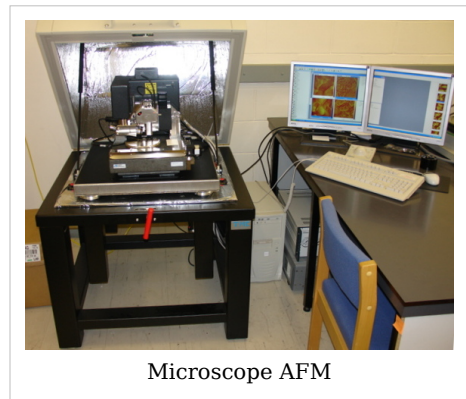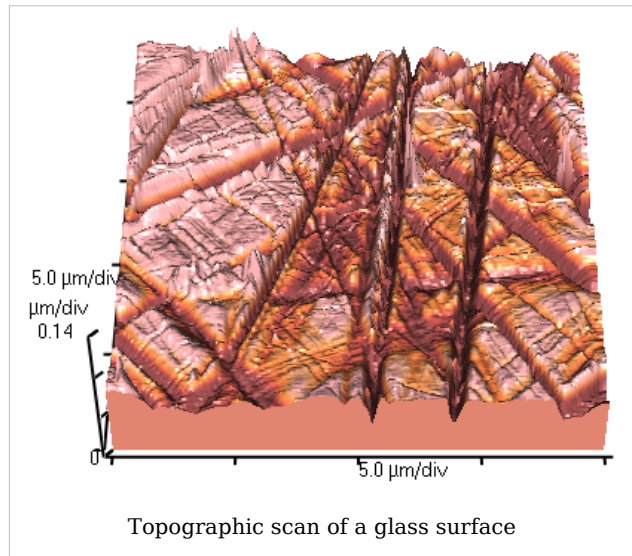
Basic principle

Part of a series of articles on

Nanotechnology

History
Implications
Applications
Regulation
Organizations
Popular culture
List of topics

Nanomaterials

Fullerene
Carbon Nanotubes
Nanoparticles

Nanomedicine

Nanotoxicology
Nanosensor

Molecular self-assembly

Self-assembled monolayer
Supramolecular assembly
DNA nanotechnology

Nanoelectronics

Molecular electronics
Nanolithography

Scanning probe microscopy

Atomic force microscope
Scanning tunneling microscope

Molecular nanotechnology

Molecular assembler
Nanorobotics
Mechanosynthesis

Nanotechnology Portal

Block Diagram of Atomic Force Microscope
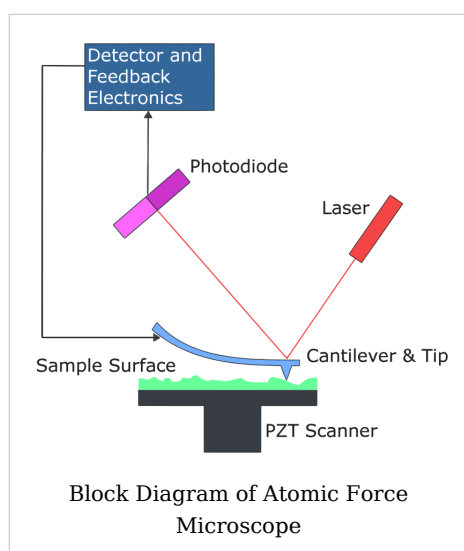
The AFM consists of a microscale cantilever with a sharp tip (probe) at its end that is used to scan the specimen surface. The cantilever is typically silicon or silicon nitride with a tip radius of curvature on the order of nanometers. When the tip is brought into proximity of a sample surface, forces between the tip and the sample lead to a deflection of the cantilever according to Hooke's law. Depending on the situation, forces that are measured in AFM include mechanical contact force, Van der Waals forces, capillary forces, chemical bonding, electrostatic forces, magnetic forces (see Magnetic force microscope (MFM)), Casimir forces, solvation forces etc. As well as force, additional quantities may simultaneously be measured through the
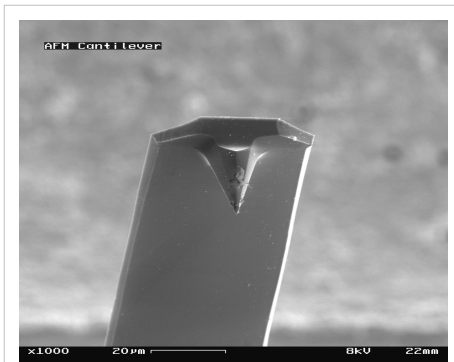
AFM cantilever (after use) in the Scanning Electron Microscope, magnification 1,000 x (image width ~ 100 micrometers)
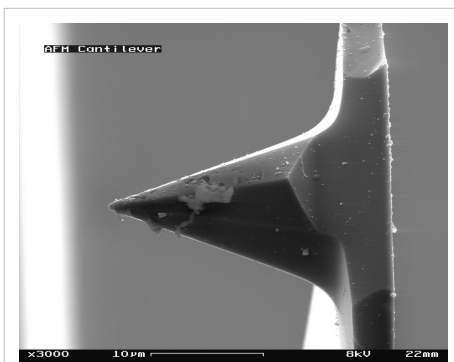
AFM cantilever (after use) in the Scanning Electron Microscope, magnification 3,000 x (image width ~ 30 micrometers)

use of specialised types of probe (see Scanning thermal microscopy, photothermal microspectroscopy, etc.). Typically, the deflection is measured using a laser spot reflected from the top surface of the cantilever into an array of photodiodes. Other methods that are used include optical interferometry, capacitive sensing or piezoresistive AFM cantilevers. These cantilevers are fabricated with piezoresistive elements that act as a strain gauge. Using a Wheatstone bridge, strain in the AFM cantilever due to deflection can be measured, but this method is not as sensitive as laser deflection or interferometry.

If the tip was scanned at a constant height, a risk would exist that the tip collides with the surface, causing damage. Hence, in most cases a feedback mechanism is employed to adjust the tip-to-sample distance to maintain a constant force between the tip and the sample. Traditionally, the sample is mounted on a piezoelectric tube, that can move the sample in the *z* direction for maintaining a constant force, and the *x* and *y* directions for scanning the sample. Alternatively a 'tripod' configuration of three piezo crystals may be employed, with each responsible for scanning in the x,y and z directions. This eliminates some of the distortion effects seen with a tube scanner. In newer designs, the tip is mounted on a vertical piezo scanner while the sample is being scanned in X and Y using another piezo block. The resulting map of the area $s = f(x,y)$ represents the topography of the sample.

The AFM can be operated in a number of modes, depending on the application. In general, possible imaging modes are divided into static (also called Contact) modes and a variety of dynamic (or non-contact) modes where the cantilever is vibrated.

Imaging modes

The primary modes of operation are static (contact) mode and dynamic mode. In the static mode operation, the static tip deflection is used as a feedback signal. Because the measurement of a static signal is prone to noise and drift, low stiffness cantilevers are used to boost the deflection signal. However, close to the surface of the sample, attractive forces can be quite strong, causing the tip to 'snap-in' to the surface. Thus static mode AFM is almost always done in contact where the overall force is repulsive. Consequently, this technique is typically called 'contact mode'. In contact mode, the force between the tip and the surface is kept constant during scanning by maintaining a constant deflection.

In the dynamic mode, the cantilever is externally oscillated at or close to its fundamental resonance frequency or a harmonic. The oscillation amplitude, phase and resonance frequency are modified by tip-sample interaction forces; these changes in oscillation with respect to the external reference oscillation provide information about the sample's

characteristics. Schemes for dynamic mode operation include frequency modulation and the more common amplitude modulation. In frequency modulation, changes in the oscillation frequency provide information about tip-sample interactions. Frequency can be measured with very high sensitivity and thus the frequency modulation mode allows for the use of very stiff cantilevers. Stiff cantilevers provide stability very close to the surface and, as a result, this technique was the first AFM technique to provide true atomic resolution in ultra-high vacuum conditions (Giessibl).

In amplitude modulation, changes in the oscillation amplitude or phase provide the feedback signal for imaging. In amplitude modulation, changes in the phase of oscillation can be used to discriminate between different types of materials on the surface. Amplitude modulation can be operated either in the non-contact or in the intermittent contact regime. In ambient conditions, most samples develop a liquid meniscus layer. Because of this, keeping the probe tip close enough to the sample for short-range forces to become detectable while preventing the tip from sticking to the surface presents a major hurdle for the non-contact dynamic mode in ambient conditions. Dynamic contact mode (also called intermittent contact or tapping mode) was developed to bypass this problem (Zhong et al.). In dynamic contact mode, the cantilever is oscillated such that the separation distance between the cantilever tip and the sample surface is modulated.

Amplitude modulation has also been used in the non-contact regime to image with atomic resolution by using very stiff cantilevers and small amplitudes in an ultra-high vacuum environment.

Tapping Mode

In *tapping mode* the cantilever is driven to oscillate up and down at near its resonance frequency by a small piezoelectric element mounted in the AFM tip holder. The amplitude of this oscillation is greater than 10 nm, typically 100 to 200 nm. Due to the interaction of forces acting on the cantilever when the tip comes close to the surface, Van der Waals force or dipole-dipole interaction, electrostatic forces, etc cause the amplitude of this oscillation to decrease as the tip gets closer to the sample. An electronic servo uses the piezoelectric actuator to control the height of the cantilever above the sample. The servo adjusts the height to maintain a set cantilever oscillation amplitude as the cantilever is scanned over the sample. A *Tapping AFM* image is therefore produced by imaging the force of the oscillating contacts of the tip with the sample surface. This is an improvement on conventional contact AFM, in which the cantilever just drags

Single polymer chains (0.4 nm thick) recorded in a tapping mode under aqueous media with different pH. Green locations of the two-chains-superposition correspond to 0.8 nm thickness (Roiter and Minko, 2005).

across the surface at constant force and can result in surface damage. Tapping mode is gentle enough even for the visualization of supported lipid bilayers or adsorbed single
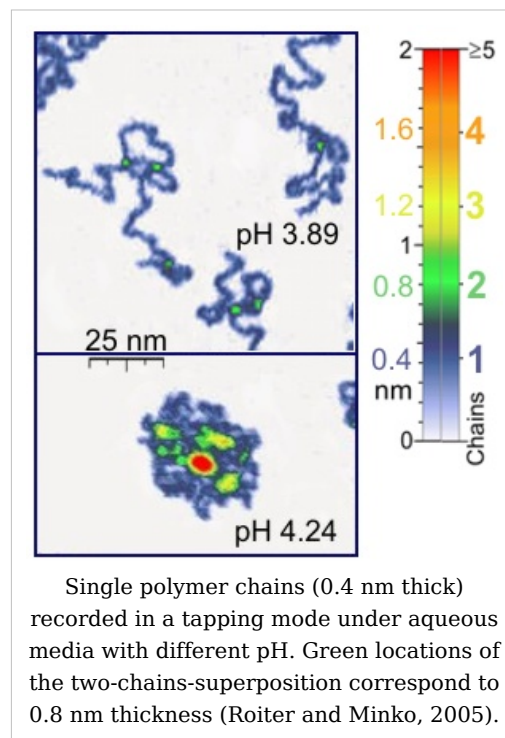
polymer molecules (for instance, 0.4 nm thick chains of synthetic polyelectrolytes) under liquid medium. At the application of proper scanning parameters, the conformation of single molecules remains unchanged for hours (Roiter and Minko, 2005).

Non-Contact Mode

Here the tip of the cantilever does not contact the sample surface. The cantilever is instead oscillated at a frequency slightly above its resonance frequency where the amplitude of oscillation is typically a few nanometers (<10nm). The van der Waals forces, which are strongest from 1nm to 10nm above the surface, or any other long range force which extends above the surface acts to decrease the resonance frequency of the cantilever. This decrease in resonance frequency combined with the feedback loop system maintains a constant oscillation amplitude or frequency by adjusting the average tip-to-sample distance. Measuring the tip-to-sample distance at each (x,y) data point allows the scanning software to construct a topographic image of the sample surface.

Non-contact mode AFM does not suffer from tip or sample degradation effects that are sometimes observed after taking numerous scans with contact AFM. This makes non-contact AFM preferable to contact AFM for measuring soft samples. In the case of rigid samples, contact and non-contact images may look the same. However, if a few monolayers of adsorbed fluid are lying on the surface of a rigid sample, the images may look quite different. An AFM operating in contact mode will penetrate the liquid layer to image the underlying surface, whereas in non-contact mode an AFM will oscillates above the adsorbed fluid layer to image both the liquid and surface.

AFM -Beam Deflection Detection

Laser light from a solid state diode is reflected off the back of the cantilever and collected by a position sensitive detector (PSD) consisting of two closely spaced photodiodes whose output signal is collected by a differential amplifier. Angular displacement of cantilever results in one photodiode collecting more light than the other photodiode, producing an output signal (the difference between the photodiode signals normalized by their sum) which is proportional to the deflection of the cantilever. It detects cantilever

AFM - Non-Contact Mode

deflections <1Å (thermal noise limited). A long beam path (several cm) amplifies changes in beam angle.

AFM Beam Deflection Detection
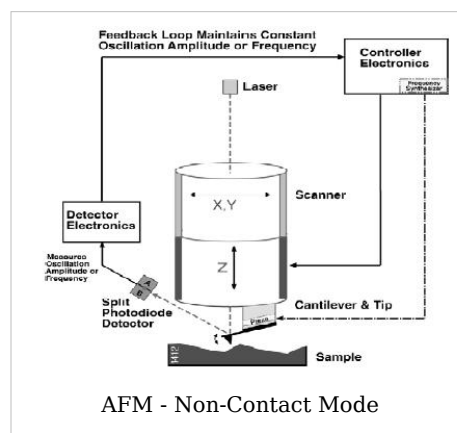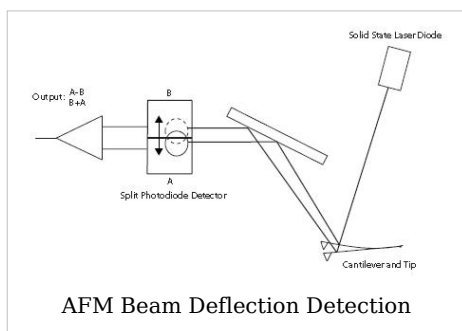
Force spectroscopy

Another major application of AFM (besides imaging) is force spectroscopy, the measurement of force-distance curves. For this method, the AFM tip is extended towards and retracted from the surface as the static deflection of the cantilever is monitored as a function of piezoelectric displacement. These measurements have been used to measure nanoscale contacts, atomic bonding, Van der Waals forces, and Casimir forces, dissolution forces in liquids and single molecule stretching and rupture forces (Hinterdorfer & Dufrêne). Forces of the order of a few pico-Newton can now be routinely measured with a vertical distance resolution of better than 0.1 nanometer.

Problems with the technique include no direct measurement of the tip-sample separation and the common need for low stiffness cantilevers which tend to 'snap' to the surface. The snap-in can be reduced by measuring in liquids or by using stiffer cantilevers, but in the latter case a more sensitive deflection sensor is needed. By applying a small dither to the tip, the stiffness (force gradient) of the bond can be measured as well (Hoffmann et al.).

Identification of individual surface atoms

The AFM can be used to image and manipulate atoms and structures on a variety of surfaces. The atom at the apex of the tip "senses" individual atoms on the underlying surface when it forms incipient chemical bonds with each atom. Because these chemical interactions subtly alter the tip's vibration frequency, they can be detected and mapped.

Physicist Oscar Custance (Osaka University, Graduate School of Engineering, Osaka, Japan) and his team used this principle to distinguish between atoms of silicon, tin and lead on an alloy surface (*Nature* 2007, 446, 64).

The trick is to first measure these forces precisely for each type of atom expected in the sample. The team found that the tip interacted most strongly with silicon atoms, and interacted 23% and 41% less strongly with tin and lead atoms, respectively. Thus, each different type of atom can be identified in the matrix as the tip is moved across the surface.

The atoms of a Sodium Chloride crystal viewed with an Atomic Force Microscope

Such a technique has been used now in biology and extended recently to cell biology. Forces corresponding to (i) the unbinding of receptor ligand couples (ii) unfolding of proteins (iii) cell adhesion at single cell scale have been gathered.

Advantages and disadvantages

The AFM has several advantages over the scanning electron microscope (SEM). Unlike the electron microscope which provides a two-dimensional projection or a two-dimensional image of a sample, the AFM provides a true three-dimensional surface profile. Additionally, samples viewed by AFM do not require any special treatments (such as metal/carbon coatings) that would irreversibly change or damage the sample. While an electron microscope needs an expensive vacuum environment for proper operation, most AFM modes can work perfectly well in ambient air or even a liquid environment. This makes it possible to study

The first Atomic Force Microscope

biological macromolecules and even living organisms. In principle, AFM can provide higher resolution than SEM. It has been shown to give true atomic resolution in ultra-high vacuum (UHV) and, more recently, in liquid environments. High resolution AFM is comparable in resolution to Scanning Tunneling Microscopy and Transmission Electron Microscopy.

A disadvantage of AFM compared with the scanning electron microscope (SEM) is the image size. The SEM can image an area on the order of millimetres by millimetres with a depth of field on the order of millimetres. The AFM can only image a maximum height on the order of micrometres and a maximum scanning area of around 150 by 150 micrometres.

Another inconvenience is that an incorrect choice of tip for the required resolution can lead to image artifacts. Traditionally the AFM could not scan images as fast as an SEM, requiring several minutes for a typical scan, while a SEM is capable of scanning at near real-time (although at relatively low quality) after the chamber is evacuated. The relatively slow rate of scanning during AFM imaging often leads to thermal drift in the image (Lapshin, 2004, 2007), making the AFM microscope less suited for measuring accurate distances between artifacts on the image. However, several fast-acting designs were suggested to increase microscope scanning productivity (Lapshin and Obyedkov, 1993) including what is being termed videoAFM (reasonable quality images are being obtained with videoAFM at video rate - faster than the average SEM). To eliminate image distortions induced by thermodrift, several methods were also proposed (Lapshin, 2004, 2007).

AFM images can also be affected by hysteresis of the piezoelectric material (Lapshin, 1995) and cross-talk between the (x,y,z) axes that may require software enhancement and filtering. Such filtering could "flatten" out real topographical features. However, newer AFM use real-time correction software (for example, feature-oriented scanning, Lapshin, 2004, 2007) or closed-loop scanners which practically eliminate these problems. Some AFM also use separated orthogonal scanners (as opposed to a single tube) which also serve to eliminate cross-talk problems.

Due to the nature of AFM probes, they cannot normally measure steep walls or overhangs. Specially made cantilevers can be modulated sideways as well as up and down (as with dynamic contact and non-contact modes) to measure sidewalls, at the cost of more expensive cantilevers and additional artifacts.
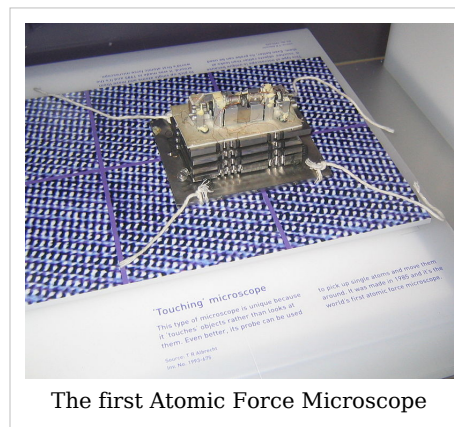
Piezoelectric Scanners

AFM scanners are made from piezoelectric material, which expands and contracts proportionally to an applied voltage. Whether they elongate or contract depends upon the polarity of the voltage applied. The scanner is constructed by combining independently operated piezo electrodes for X, Y, & Z into a single tube, forming a scanner which can manipulate samples and probes with extreme precision in 3 dimensions.

Scanners are characterized by their sensitivity which is the ratio of piezo movement to piezo voltage, i.e. by how much the piezo material extends or contracts per applied volt. Because of differences in material or size, the sensitivity varies from scanner to scanner.

Piezoelectric Scanner

Sensitivity varies non-linearly with respect to scan size. Piezo scanners exhibit more sensitivity at the end than at the beginning of a scan. This causes the forward and reverse scans to behave differently and display hysteresis between the two scan directions. This can be corrected by applying a non-linear voltage to the piezo electrodes to cause linear scanner movement and calibrating the scanner accordingly.

The sensitivity of piezoelectric materials decreases exponentially with time. This causes most of the change in sensitivity to occur in the initial stages of the scanner's life. Piezoelectric scanners are run for approximately 48 hours before they are shipped from the factory so that they are past the point where we can expect large changes in sensitivity. As the scanner ages, the sensitivity will change less with time and the scanner would seldom require recalibration.

See also

- Interfacial force microscope
- Friction force microscope
- Scanning tunneling microscope
- Scanning probe microscopy
- Scanning voltage microscopy

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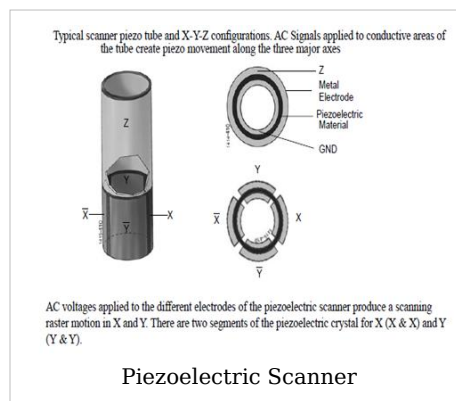
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X-ray microscope

An **X-ray microscope** uses electromagnetic radiation in the soft X-ray band to produce images of very small objects.

Unlike visible light, X-rays do not reflect or refract easily, and they are invisible to the human eye. Therefore the basic process of an X-ray microscope is to expose film or use a charge-coupled device (CCD) detector to detect X-rays that pass through the specimen. It is a contrast imaging technology using the difference in absorption of soft x-ray in the water window region (wavelength region: 2.3 - 4.4 nm, photon energy region: 0.28 - 0.53 keV) by the carbon atom (main element composing the living cell) and the oxygen atom (main element for water).

Early X-ray microscopes by Paul Kirkpatrick and Albert Baez used grazing-incidence reflective optics to focus the X-rays, which grazed X-rays off parabolic curved mirrors at a very high angle of incidence. An alternative method of focusing X-rays is to use a tiny fresnel zone plate of concentric gold or nickel rings on a silicon dioxide substrate. Sir Lawrence Bragg produced some of the first usable X-ray images with his apparatus in the late 1940's.

In the 1950's Newberry produced a shadow X-ray microscope which placed the specimen between the source and a target plate, this became the basis for the first commercial X-ray microscopes from the General Electric Company.

The Advanced Light Source (ALS)[1] in Berkeley CA is home to XM-1 (http://www.cxro.lbl.gov/BL612/
), a full field soft X-ray microscope operated by the Center for X-ray Optics [2] and dedicated to various applications in modern nanoscience, such as nanomagnetic materials, environmental and materials sciences and biology. XM-1 uses an X-ray lens to focus X-rays on a CCD, in a manner similar to an optical microscope. XM-1 still holds the world record in spatial resolution with Fresnel zone plates down to 15nm and is able to combine high spatial resolution with a sub-100ps time resolution to study e.g. ultrafast spin dynamics.

Indirect drive laser inertial confinement fusion uses a "hohlraum" which is irradiated with laser beam cones from either side on it its inner surface to bathe a fusion microcapsule inside with smooth high intensity X-rays. The highest energy X-rays which penetrate the hohlraum can be visualized using an X-ray microscope such as here, where X-radiation is represented in orange/red.

The ALS is also home to the world's first soft x-ray microscope designed for biological and biomedical research. This new instrument, XM-2 was designed and built by scientists from the National Center for X-ray Tomography (http://ncxt.lbl.gov). XM-2 is capable of producing 3-Dimensional tomograms of cells.

Sources of soft X-rays suitable for microscopy, such as synchrotron radiation sources, have fairly low brightness of the required wavelengths, so an alternative method of image formation is scanning transmission soft X-ray microscopy. Here the X-rays are focused to a point and the sample is mechanically scanned through the produced focal spot. At each point the transmitted X-rays are recorded with a detector such as a proportional counter or an avalanche photodiode. This type of Scanning Transmission X-ray Microscope (STXM)

was first developed by researchers at Stony Brook University and was employed at the National Synchrotron Light Source at Brookhaven National Laboratory.

The resolution of X-ray microscopy lies between that of the optical microscope and the electron microscope. It has an advantage over conventional electron microscopy in that it can view biological samples in their natural state. Electron microscopy is widely used to obtain images with nanometer level resolution but the relatively thick living cell cannot be observed as the sample has to be chemically fixed, dehydrated, embedded in resin, then sliced ultra thin. However, it should be mentioned that cryo-electron microscopy allows the observation of biological specimens in their hydrated natural state. Until now, resolutions of 30 nanometer are possible using the Fresnel zone plate lens which forms the image using the soft x-rays emitted from a synchrotron. Recently, more researchers have begun to use the soft x-rays emitted from laser-produced plasma rather than synchrotron radiation.

Additionally, X-rays cause fluorescence in most materials, and these emissions can be analyzed to determine the chemical elements of an imaged object. Another use is to generate diffraction patterns, a process used in X-ray crystallography. By analyzing the internal reflections of a diffraction pattern (usually with a computer program), the three-dimensional structure of a crystal can be determined down to the placement of individual atoms within its molecules. X-ray microscopes are sometimes used for these analyses because the samples are too small to be analyzed in any other way.

See also

- Synchrotron X-ray tomographic microscopy

External links

- Application of X-ray microscopy in analysis of living hydrated cells [18]
- Hard X-ray microbeam experiments with a sputtered-sliced Fresnel zone plate and its applications [3]
- Scientific applications of soft x-ray microscopy [4]
- Microarrays products [5]
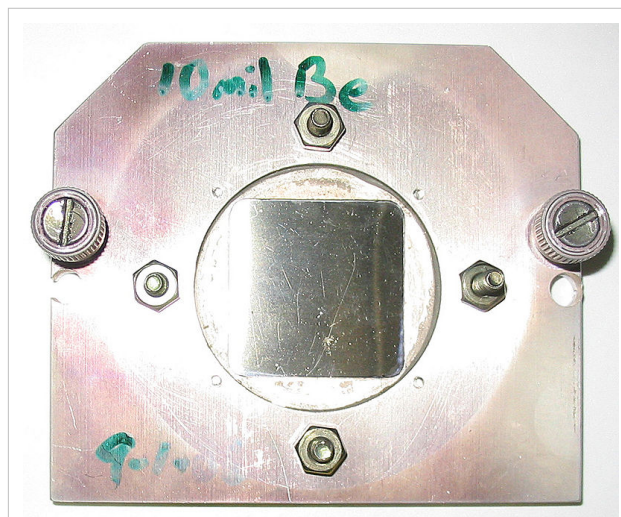
A square beryllium foil mounted in a steel case to be used as a window between a vacuum chamber and an X-ray microscope. Beryllium, due to its low Z number is highly transparent to X-rays.

References

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[4] http://www.cxro.lbl.gov/BL612/index.php?content=research.html

[5] http://www.ibio.co.il/Products.aspx?level=2&prodID=17

Fluorescence microscope

A **fluorescence microscope** (colloquially synonymous with *epifluorescent microscope*) is a light microscope used to study properties of organic or inorganic substances using the phenomena of fluorescence and phosphorescence instead of, or in addition to, reflection and absorption.[1] [2]

A fluorescent microscope (Olympus BX61), coupled with a digital camera.

Technique

In most cases, a component of interest in the specimen is specifically labeled with a fluorescent molecule called a fluorophore (such as green fluorescent protein (GFP), fluorescein or DyLight 488).[1] The specimen is illuminated with light of a specific wavelength (or wavelengths) which is absorbed by the fluorophores, causing them to emit longer wavelengths of light (of a different color than the absorbed light). The illumination light is separated from the much weaker emitted fluorescence through the use of an emission filter. Typical components of a fluorescence microscope are the light source (xenon arc lamp or mercury-vapor lamp), the excitation filter, the dichroic mirror (or dichromatic beamsplitter), and the emission filter (see figure below). The filters and the dichroic are chosen to match the spectral excitation and emission characteristics of the fluorophore used to label the specimen.[1] In this manner, a single fluorophore (color) is imaged at a time. Multi-color images of several fluorophores must be composed by combining several single-color images.[1]

An inverted fluorescent microscope (Nikon TE2000). Note the orange plate that allows the user to look at the sample while protecting his eyes from the excitation UV light.

Most fluorescence microscopes in use are epifluorescence microscopes (i.e. excitation and observation of the fluorescence are from above (*epi*–) the specimen). These microscopes have become an important part in the field of biology, opening the doors for more advanced microscope designs, such as the confocal laser scanning microscope and the total internal reflection fluorescence microscope (TIRF). The Vertico SMI combining localisation microscopy with spatially modulated illumination uses standard fluorescence dyes and reaches an optical resolution below 10 nanometers (1 nanometer = 1 nm = 1×10^{-9} m).

Fluorophores lose their ability to fluoresce as they are illuminated in a process called photobleaching. Special care must be taken to prevent photobleaching through the use of more robust fluorophores, by minimizing illumination, or by introducing a scavenger system to reduce the rate of photobleaching.

Epifluorescence microscopy

Schematic of a fluorescence microscope.

Epifluorescence microscopy is a method of fluorescence microscopy that is widely used in life sciences. The excitatory light is passed from above (or, for inverted microscopes, from below), through the objective and then onto the specimen instead of passing it first through the specimen. (In the latter case the transmitted excitatory light reaches the objective together with light emitted from the specimen). The fluorescence in the specimen gives rise to emitted light which is focused to the detector by the same objective that is used for the excitation. A filter between the objective and the detector filters out the excitation light from fluorescent light. Since most of the excitatory light is transmitted through the specimen, only reflected excitatory light reaches the objective together with the emitted light and this method therefore gives an improved signal to noise ratio. A common use in biology is to apply fluorescent or fluorochrome stains to the specimen in order to image a protein or other molecule of interest.

Gallery
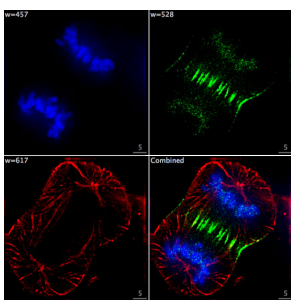
Epifluorescent imaging of the three components in a dividing human cancer cell. DNA is stained blue, a protein called INCENP is green, and the microtubules are red. Each fluorophore is imaged separately using a different combination of excitation and emission filters, and the images are captured sequentially using a digital CCD camera, then overlaid to give a complete image.
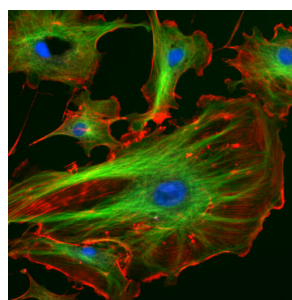
Endothelial cells under the microscope. Nuclei are stained blue with DAPI, microtubules are marked green by an antibody bound to FITC and actin filaments are labelled red with phalloidin bound to TRITC. Bovine pulmonary artery endothelial (BPAE) cells
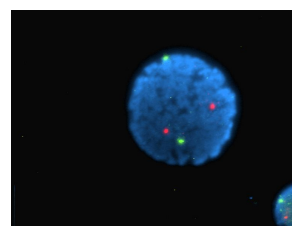
human lymphocyte nucleus stained with DAPI with chromosome 13 (green) and 21 (red) centromere probes hybrydized (Fluorescent in situ hybridization (FISH))
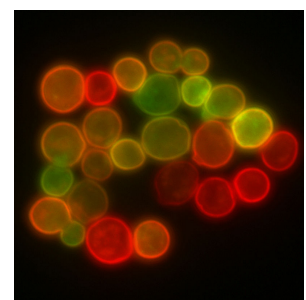
Yeast cell membrane visualized by some membrane proteins fused with RFP and GFP fluorescent markers. Imposition of light from both of markers results in yellow colour.

See also

- Microscope
- Mercury-vapor lamp
- Xenon arc lamp
- Stokes shift

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External links

- WikiScope (http://wikiscope.org)
- Fluorophores.org (http://www.fluorophores.org) - Database of fluorescent dyes.

Fluorescence correlation spectroscopy

Fluorescence correlation spectroscopy (**FCS**) is a common technique used by physicists, chemists, and biologists to experimentally characterize the dynamics of fluorescent species (e.g. single fluorescent dye molecules in nanostructured materials, autofluorescent proteins in living cells, etc.). Although the name indicates a specific link to fluorescence, the method is used today also for exploring other forms of luminescence (like reflections, luminescence from gold-beads or quantum dots or phosphorescent species). The "spectroscopy" in the name is not readily found as in common usage a spectrum is generally understood to be a frequency spectrum. The autocorrelation is a genuine form of spectrum, however: It is the time-spectrum generated from the power spectrum (via inverse fourier transform).

Commonly, FCS is employed in the context of optical microscopy, in particular confocal or two photon microscopy. In these techniques light is focused on a sample and the measured fluorescence intensity fluctuations (due to diffusion, physical or chemical reactions, aggregation, etc.) are analyzed using the temporal autocorrelation. Because the measured property is essentially related to the magnitude and/or the amount of fluctuations, there is an optimum measurement regime at the level when individual species enter or exit the observation volume (or turn on and off in the volume). When too many entities are measured at the same time the overall fluctuations are small in comparison to the total signal and may not be resolvable - in the other direction, if the individual fluctuation-events are too sparse in time, one measurement may take prohibitively too long. FCS is in a way the fluorescent counterpart to dynamic light scattering, which uses coherent light scattering, instead of (incoherent) fluorescence.

When an appropriate model is known, FCS can be used to obtain quantitative information such as

- diffusion coefficients
- hydrodynamic radii
- average concentrations
- kinetic chemical reaction rates
- singlet-triplet dynamics

Because fluorescent markers come in a variety of colors and can be specifically bound to a particular molecule (e.g. proteins, polymers, metal-complexes, etc.), it is possible to study the behavior of individual molecules (in rapid succession in composite solutions). With the development of sensitive detectors such as avalanche photodiodes the detection of the fluorescence signal coming from individual molecules in highly dilute samples has become practical. With this emerged the possibility to conduct FCS experiments in a wide variety of specimens, ranging from materials science to biology. The advent of engineered cells with genetically tagged proteins (like green fluorescent protein) has made FCS a common tool for studying molecular dynamics in living cells.

History

Signal-correlation techniques have first been experimentally applied to fluorescence in 1972 by Magde, Elson, and Webb[1] , who are therefore commonly credited as the "inventors" of FCS. The technique was further developed in a group of papers by these and other authors soon after, establishing the theoretical foundations and types of applications.[2] [3] [4] See Thompson (1991)[5] for a review of that period.

Beginning in 1993[6] , a number of improvements in the measurement techniques--notably using confocal microscopy, and then two photon microscopy--to better define the measurement volume and reject background greatly improved the signal-to-noise and allowed single molecule sensitivity.[7] [8] Since then, there has been a renewed interest in FCS, and as of August 2007 there has been over 3,000 papers using FCS found in Web of Science. See Krichevsky and Bonnet[9] for a recent review. In addition, there has been a flurry of activity extending FCS in various ways, for instance to laser scanning and spinning disk confocal microscopy (from a stationary, single point measurement), in using cross-correlation (FCCS) between two fluorescent channels instead of autocorrelation, and in using Förster Resonance Energy Transfer (FRET) instead of fluorescence.

Typical FCS setup

The typical FCS setup consists of a laser line (wavelengths ranging typically from 405 - 633 nm (cw), and from 690 - 1100 nm (pulsed)), which is reflected into a microscope objective by a dichroic mirror. The laser beam is focused in the sample, which contains fluorescent particles (molecules) in such high dilution, that only few are within the focal spot (usually 1 - 100 molecules in one fL). When the particles cross the focal volume, they fluoresce. This light is collected by the same objective and, because it is red-shifted with respect to the excitation light it passes the dichroic reaching a detector, typically a photomultiplier tube or avalanche photodiode detector. The resulting electronic signal can be stored either directly as an intensity versus time trace to be analyzed at a later point, or, computed to generate the autocorrelation directly (which requires special acquisition cards). The FCS curve by itself only represents a time-spectrum. Conclusions on physical phenomena have to be extracted from there with appropriate models. The parameters of interest are found after fitting the autocorrelation curve to modeled functional forms. [10] The setup is shown in Figure 1.

The Measurement Volume

The measurement volume is a convolution of illumination (excitation) and detection geometries, which result from the optical elements involved. The resulting volume is described mathematically by the point spread function (or PSF), it is essentially the image of a point source. The PSF is often described as an ellipsoid (with unsharp boundaries) of few hundred nanometers in focus diameter, and almost one micrometre along the optical axis. The shape varies significantly (and has a large impact on the resulting FCS curves) depending on the quality of the optical elements (it is crucial to avoid astigmatism and to check the real shape of the PSF on the instrument). In the case of confocal microscopy, and for small pinholes (around one Airy unit), the PSF is well approximated by Gaussians:

$$PSF(r, z) = I_0 e^{-2r^2/\omega_{xy}^2} e^{-2z^2/\omega_z^2}$$

where I_0 is the peak intensity, r and z are radial and axial position, and ω_{xy} and ω_z are the radial and axial radii, and $\omega_z > \omega_{xy}$. This Gaussian form is assumed in deriving the functional form of the autocorrelation.

Typically ω_{xy} is 200-300 nm, and ω_z is **2-6** times larger.[11] One common way of calibrating the measurement volume parameters is to perform FCS on a species with known diffusion coefficient and concentration (see below). Diffusion coefficients for common fluorophores in water are given in a later section.

The Gaussian approximation works to varying degrees depending on the optical details, and corrections can sometimes be applied to offset the errors in approximation.[12]

Autocorrelation Function

The (temporal) autocorrelation function is the correlation of a time series with itself shifted by time τ, as a function of τ:

$$G(\tau) = \frac{\langle \delta I(t) \delta I(t+\tau) \rangle}{\langle I(t) \rangle^2} = \frac{\langle I(t) I(t+\tau) \rangle}{\langle I(t) \rangle^2} - 1$$

where $\delta I(t) = I(t) - \langle I(t) \rangle$ is the deviation from the mean intensity. The normalization (denominator) here is the most commonly used for FCS, because then the correlation at $\tau = 0$, $G(0)$, is related to the average number of particles in the measurement volume.

Interpreting the Autocorrelation Function

To extract quantities of interest, the autocorrelation data can be fitted, typically using a nonlinear least squares algorithm. The fit's functional form depends on the type of dynamics (and the optical geometry in question).

Normal Diffusion

The fluorescent particles used in FCS are small and thus experience thermal motions in solution. The simplest FCS experiment is thus normal 3D diffusion, for which the autocorrelation is:

$$G(\tau) = G(0) \frac{1}{(1 + (\tau/\tau_D))(1 + a^{-2}(\tau/\tau_D))^{1/2}} + G(\infty)$$

where $a = \omega_z/\omega_{xy}$ is the ratio of axial to radial e^{-2} radii of the measurement volume, and τ_D is the characteristic residence time. This form was derived assuming a Gaussian measurement volume. Typically, the fit would have three free parameters--G(0), $G(\infty)$, and τ_D--from which the diffusion coefficient and fluorophore concentration can be obtained.

With the normalization used in the previous section, G(0) gives the mean number of diffusers in the volume <N>, or equivalently--with knowledge of the observation volume size--the mean concentration:

$$G(0) = \frac{1}{<N>} = \frac{1}{V_{eff} <C>},$$

where the effective volume is found from integrating the Gaussian form of the measurement volume and is given by:

$$V_{eff} = \pi^{3/2} \omega_{xy}^2 \omega_z.$$

τ_D gives the diffusion coefficient: $D = \omega_{xy}^2/4\tau_D$.

Anomalous diffusion

If the diffusing particles are hindered by obstacles or pushed by a force (molecular motors, flow, etc.) the dynamics is often not sufficiently well-described by the normal diffusion model, where the mean squared displacement (MSD) grows linearly with time. Instead the diffusion may be better described as anomalous diffusion, where the temporal dependenc of the MSD is non-linear as in the power-law:

$$MSD = 6D_a t^\alpha$$

where D_a is an anomalous diffusion coefficient. "Anomalous diffusion" commonly refers only to this very generic model, and not the many other possibilities that might be described as anomalous. Also, a power law is, in a strict sense, the expected form only for a narrow range of rigorously defined systems, for instance when the distribution of obstacles is fractal. Nonetheless a power law can be a useful approximation for a wider range of systems.

The FCS autocorrelation function for anomalous diffusion is:

$$G(\tau) = G(0)\frac{1}{(1 + (\tau/\tau_D)^\alpha)(1 + a^{-2}(\tau/\tau_D)^\alpha)^{1/2}} + G(\infty),$$

where the anomalous exponent α is the same as above, and becomes a free parameter in the fitting.

Using FCS, the anomalous exponent has been shown to be an indication of the degree of molecular crowding (it is less than one and smaller for greater degrees of crowding)[13].

Polydisperse diffusion

If there are diffusing particles with different sizes (diffusion coefficients), it is common to fit to a function that is the sum of single component forms:

$$G(\tau) = G(0)\sum_i \frac{\alpha_i}{(1 + (\tau/\tau_{D,i}))(1 + a^{-2}(\tau/\tau_{D,i}))^{1/2}} + G(\infty)$$

where the sum is over the number different sizes of particle, indexed by i, and α_i gives the weighting, which is related to the quantum yield and concentration of each type. This introduces new parameters, which makes the fitting more difficult as a higher dimensional space must be searched. Nonlinear least square fitting typically becomes unstable with even a small number of $\tau_{D,i}$ s. A more robust fitting scheme, especially useful for polydisperse samples, is the Maximum Entropy Method[14].

Diffusion with flow

With diffusion together with a uniform flow with velocity v in the lateral direction, the autocorrelation is[15]:

$$G(\tau) = G(0)\frac{1}{(1 + (\tau/\tau_D))(1 + a^{-2}(\tau/\tau_D))^{1/2}} \times \exp[-(\tau/\tau_v)^2 \times \frac{1}{1 + \tau/\tau_D}] + G(\infty)$$

where $\tau_v = \omega_{xy}/v$ is the average residence time if there is only a flow (no diffusion).

Chemical relaxation

A wide range of possible FCS experiments involve chemical reactions that continually fluctuate from equilibrium because of thermal motions (and then "relax"). In contrast to diffusion, which is also a relaxation process, the fluctuations cause changes between states of different energies. One very simple system showing chemical relaxation would be a stationary binding site in the measurement volume, where particles only produce signal when bound (e.g. by FRET, or if the diffusion time is much faster than the sampling interval). In this case the autocorrelation is:

$$G(\tau) = G(0) \exp(-\tau/\tau_B) + G(\infty)$$

where

$$\tau_B = (k_{on} + k_{off})^{-1}$$

is the relaxation time and depends on the reaction kinetics (on and off rates), and:

$$G(0) = \frac{1}{\langle N \rangle} \frac{k_{on}}{k_{off}} = \frac{1}{\langle N \rangle} K$$

is related to the equilibrium constant K.

Most systems with chemical relaxation also show measureable diffusion as well, and the autocorrelation function will depend on the details of the system. If the diffusion and chemical reaction are decoupled, the combined autocorrelation is the product of the chemical and diffusive autocorrelations.

Triplet State Correction

The autocorrelations above assume that the fluctuations are not due to changes in the fluorescent properties of the particles. However, for the majority of (bio)organic fluorophores--e.g. green fluorescent protein, rhodamine, Cy3 and Alexa Fluor dyes--some fraction of illuminated particles are excited to a triplet state (or other non-radiative decaying states) and then do not emit photons for a characteristic relaxation time τ_F. Typically τ_F is on the order of microseconds, which is usually smaller than the dynamics of interest (e.g. τ_D) but large enough to be measured. A multiplicative term is added to the autocorrelation account for the triplet state. For normal diffusion:

$$G(\tau) = G(0) \frac{1 - F + F e^{-\tau/\tau_F}}{1 - F} \frac{1}{(1 + (\tau/\tau_{D,i}))(1 + a^{-2}(\tau/\tau_{D,i}))^{1/2}} + G(\infty)$$

where F is the fraction of particles that have entered the triplet state and τ_F is the corresponding triplet state relaxation time. If the dynamics of interest are much slower than the triplet state relaxation, the short time component of the autocorrelation can simply be truncated and the triplet term is unnecessary.

Common fluorescent probes

The fluorescent species used in FCS is typically a biomolecule of interest that has been tagged with a fluorophore (using immunohistochemistry for instance), or is a naked fluorophore that is used to probe some environment of interest (e.g. the cytoskeleton of a cell). The following table gives diffusion coefficients of some common fluorophores in water at room temperature, and their excitation wavelengths.

Fluorescent dye	D (x10^{-10} m^2 s^{-1})	Excitation wavelength (nm)	Reference

Rhodamine 6G	2.8, 3.0, 4.14 ± 0.05 @ 25.00 °C	514	[16] [17] [18]
Rhodamine 110	2.7	488	[19]
Tetramethyl rhodamine	2.6	543	
Cy3	2.8	543	
Cy5	2.5, 3.7 ± 0.15 @ 25.00 °C	633	[20] [21]
carboxyfluorescein	3.2	488	
Alexa-488	1.96	488	[22]
Atto655-maleimide	4.07 ± 0.1 @ 25.00 °C	663	[23]
Atto655-carboxylicacid	4.26 ± 0.08 @ 25.00 °C	663	[24]
2□, 7□-difluorofluorescein (Oregon Green488)	4.11 ± 0.06 @ 25.00 °C	498	[25]

Variations of FCS

FCS almost always refers to the single point, single channel, temporal autocorrelation measurement, although the term "fluorescence correlation spectroscopy" out of its historical scientific context implies no such restriction. FCS has been extended in a number of variations by different researchers, with each extension generating another name (usually an acronym).

Fluorescence Cross-Correlation Spectroscopy (FCCS)

FCS is sometimes used to study molecular interactions using differences in diffusion times (e.g. the product of an association reaction will be larger and thus have larger diffusion times than the reactants individually); however, FCS is relatively insensitive to molecular mass as can be seen from the following equation relating molecular mass to the diffusion time of globular particles (e.g. proteins):

$$\tau_D = \frac{3\pi\omega_{xy}^2\eta}{2kT}(M)^{1/3}$$

where η is the viscosity of the sample and M is the molecular mass of the fluorescent species. In practice, the diffusion times need to be sufficiently different--a factor of at least **1.6**--which means the molecular masses must differ by a factor of **4**.[26] Dual color fluorescence cross-correlation spectroscopy (FCCS) measures interactions by cross-correlating two or more fluorescent channels (one channel for each reactant), which distinguishes interactions more sensitively than FCS, particularly when the mass change in the reaction is small.

Two- and three- photon FCS excitation

Several advantages in both spatial resolution and minimizing photodamage/photobleaching in organic and/or biological samples are obtained by two-photon or three-photon excitation FCS[27] [28] [29] [30] [31] .

FRET-FCS

Another FCS based approach to studying molecular interactions uses fluorescence resonance energy transfer (FRET) instead of fluorescence, and is called FRET-FCS.[32] With FRET, there are two types of probes, as with FCCS; however, there is only one channel and light is only detected when the two probes are very close--close enough to ensure an interaction. The FRET signal is weaker than with fluorescence, but has the advantage that there is only signal during a reaction (aside from autofluorescence).

Image Correlation Spectroscopy (ICS)

When the motion is slow (in biology, for example, diffusion in a membrane), getting adequate statistics from a single-point FCS experiment may take a prohibitively long time. More data can be obtained by performing the experiment in multiple spatial points in parallel, using a laser scanning confocal microscope. This approach has been called Image Correlation Spectroscopy (ICS)[33] . The measurements can then be averaged together.

Another variation of ICS performs a spatial autocorrelation on images, which gives information about the concentration of particles[34] . The correlation is then averaged in time.

A natural extension of the temporal and spatial correlation versions is spatio-temporal ICS (STICS) [35] . In STICS there is no explicit averaging in space or time (only the averaging inherent in correlation). In systems with non-isotropic motion (e.g. directed flow, asymmetric diffusion), STICS can extract the directional information. A variation that is closely related to STICS (by the Fourier transform) is k-space Image Correlation Spectroscopy (kICS).[36]

There are cross-correlation versions of ICS as well.[33]

Scanning FCS variations

Some variations of FCS are only applicable to serial scanning laser microscopes. Image Correlation Spectroscopy and its variations all were implemented on a scanning confocal or scanning two photon microscope, but transfer to other microscopes, like a spinning disk confocal microscope. Raster ICS (RICS)[37] , and position sensitive FCS (PSFCS)[38] incorporate the time delay between parts of the image scan into the analysis. Also, low dimensional scans (e.g. a circular ring)[39] --only possible on a scanning system--can access time scales between single point and full image measurements. Scanning path has also been made to adaptively follow particles.[40]

Spinning disk FCS, and spatial mapping

Any of the image correlation spectroscopy methods can also be performed on a spinning disk confocal microscope, which in practice can obtain faster imaging speeds compared to a laser scanning confocal microscope. This approach has recently been applied to diffusion in a spatially varying complex environment, producing a pixel resolution map of diffusion coefficient.[41] . The spatial mapping of diffusion with FCS has subsequently been extended to TIRF system.[42] Spatial mapping of dynamics using correlation techniques had been applied before, but only at sparse points[43] or at coarse resolution[35] .

Total internal reflection FCS

Total internal reflection fluorescence (TIRF) is a microscopy approach that is only sensitive to a thin layer near the surface of a coverslip, which greatly minimizes background fluorscence. FCS has been extended to that type of microscope, and is called TIR-FCS[44] . Because the fluorescence intensity in TIRF falls off exponentially with distance from the coverslip (instead of as a Gaussian with a confocal), the autocorrelation function is different.

Other fluorescent dynamical approaches

There are two main non-correlation alternatives to FCS that are widely used to study the dynamics of fluorescent species.

Fluorescence recovery after photobleaching (FRAP)

In FRAP, a region is briefly exposed to intense light, irrecoverably photobleaching fluorophores, and the fluorescence recovery due to diffusion of nearby (non-bleached) fluorophores is imaged. A primary advantage of FRAP over FCS is the ease of interpreting qualitative experiments common in cell biology. Differences between cell lines, or regions of a cell, or before and after application of drug, can often be characterized by simple inspection of movies. FCS experiments require a level of processing and are more sensitive to potentially confounding influences like: rotational diffusion, vibrations, photobleaching, dependence on illumination and fluorescence color, inadequate statistics, etc. It is much easier to change the measurement volume in FRAP, which allows greater control. In practice, the volumes are typically larger than in FCS. While FRAP experiments are typically more qualitative, some researchers are studying FRAP quantitatively and including binding dynamics.[45] A disadvantage of FRAP in cell biology is the free radical perturbation of the cell caused by the photobleaching. It is also less versatile, as it cannot measure concentration or rotational diffusion, or co-localization. FRAP requires a significantly higher concentration of fluorophores than FCS.

Particle tracking

In particle tracking, the trajectories of a set of particles are measured, typically by applying particle tracking algorithms to movies.[46] Particle tracking has the advantage that all the dynamical information is maintained in the measurement, unlike FCS where correlation averages the dynamics to a single smooth curve. The advantage is apparent in systems showing complex diffusion, where directly computing the mean squared displacement allows straightforward comparison to normal or power law diffusion. To apply particle tracking, the particles have to be distinguishable and thus at lower concentration than

required of FCS. Also, particle tracking is more sensitive to noise, which can sometimes affect the results unpredictably.

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See also

- Confocal microscopy
- Fluorescence cross-correlation spectroscopy
- FRET
- Dynamic light scattering
- Diffusion coefficient

External links

- Single-molecule spectroscopic methods (http://dx.doi.org/10.1016/j.sbi.2004.09.004)
- FCS Classroom (http://www.fcsxpert.com/classroom)

Fluorescence cross-correlation spectroscopy

Fluorescence cross-correlation spectroscopy (FCCS) was introduced by Eigen and Rigler in 1994 and experimentally realized by Schwille in 1997. It extends the fluorescence correlation spectroscopy (FCS) procedure by introducing high sensitivity for distinguishing fluorescent particles which have a similar diffusion coefficient. FCCS uses two species which are independently labelled with two spectrally separated fluorescent probes. These fluorescent probes are excited and detected by two different laser light sources and detectors commonly known as green and red respectively. Both laser light beams are focused into the sample and tuned so that they overlap to form a superimposed confocal observation volume.

The normalized cross-correlation function is defined for two fluorescent species G and R which are independent green, G and red, R channels as follows:

$$G_{GR}(\tau) = 1 + \frac{<\delta I_G(t)\delta I_R(t+\tau)>}{<I_G(t)><I_R(t)>} = \frac{<I_G(t)I_R(t+\tau)>}{<I_G(t)><I_R(t)>}$$

where differential fluorescent signals δI_G at a specific time, t and δI_R at a delay time, τ later is correlated with each other.

Modeling

Cross-correlation curves are modeled according to a slightly more complicated mathematical function than applied in FCS. First of all, the effective superimposed observation volume in which the G and R channels form a single observation volume, $V_{eff,RG}$ in the solution:

$$V_{eff,RG} = \pi^{3/2}(\omega_{xy,G}^2 + \omega_{xy,R}^2)(\omega_{z,G}^2 + \omega_{z,R}^2)^{1/2}/2^{3/2}$$

where $\omega_{xy,G}^2$ and $\omega_{xy,R}^2$ are radial parameters and $\omega_{z,G}$ and $\omega_{z,R}$ are the axial parameters for the G and R channels respectively.

The diffusion time, $\tau_{D,GR}$ for a doubly (G and R) fluorescent species is therefore described as follows:

$$\tau_{D,GR} = \frac{\omega_{xy,G}^2 + \omega_{xy,R}^2}{8D_{GR}}$$

where D_{GR} is the diffusion coefficient of the doubly fluorescent particle.

The cross-correlation curve generated from diffusing doubly labelled fluorescent particles can be modelled in separate channels as follows:

$$G_G(\tau) = 1 + \frac{(<C_G> Diff_k(\tau) + <C_{GR}> Diff_k(\tau))}{V_{eff,GR}(<C_G> + <C_{GR}>)^2}$$

$$G_R(\tau) = 1 + \frac{(<C_R> Diff_k(\tau) + <C_{GR}> Diff_k(\tau))}{V_{eff,GR}(<C_R> + <C_{GR}>)^2}$$

In the ideal case, the cross-correlation function is proportional to the concentration of the doubly labeled fluorescent complex:

$$G_{GR}(\tau) = 1 + \frac{<C_{GR}> Diff_{GR}(\tau)}{V_{eff}(<C_G> + <C_{GR}>)(<C_R> + <C_{GR}>)}$$

with $Diff_k(\tau) = \dfrac{1}{(1 + \frac{\tau}{\tau_{D,i}})(1 + a^{-2}(\frac{\tau}{\tau_{D,i}})^{1/2}}$

Contrary to FCS, the intercept of the cross-correlation curve does not yield information about the doubly labelled fluorescent particles in solution.

See also

- Fluorescence correlation spectroscopy
- Dynamic light scattering
- Fluorescence spectroscopy
- Diffusion coefficient

External links

- FCS Classroom [1]

References

[1] http://www.fcsxpert.com/classroom

Forster resonance energy transfer

1. REDIRECT Förster resonance energy transfer

Neutron scattering

Neutron scattering encompasses all scientific techniques whereby the deflection of neutron radiation is used as a scientific probe. Neutrons readily interact with atomic nuclei and magnetic fields from unpaired electrons, making a useful probe of both structure and magnetic order. Neutron Scattering falls into two basic categories - elastic and inelastic. Elastic scattering is when a neutron interacts with a nucleus or electronic magnetic field but does not leave it in an excited state, meaning the emitted neutron has the same energy as the injected neutron. Scattering processes that involve an energetic excitation or relaxation by the neutron are inelastic: the injected neutron's energy is used or increased to create an excitation or by absorbing the excess energy from a relaxation, and consequently the emitted neutron's energy is reduced or increased respectively.

For several good reasons, moderated neutrons provide an ideal tool for the study of almost all forms of condensed matter. Firstly, they are readily produced at a nuclear research reactor or a spallation source. Normally in such processes neutrons are however produced with much higher energies than are needed. Therefore moderators are generally used which slow the neutrons down and therefore produce wavelengths that are comparable to the atomic spacing in solids and liquids, and kinetic energies that are comparable to those of dynamic processes in materials. Moderators can be made from Aluminium and filled with liquid hydrogen (for very long wavelength neutrons) or liquid methane (for shorter wavelength neutrons). Fluxes of 10^7/s - 10^8/s are not atypical in most neutron sources from any given moderator.

The neutrons cause pronounced interference and energy transfer effects in scattering experiments. Unlike an x-ray photon with a similar wavelength, which interacts with the electron cloud surrounding the nucleus, neutrons interact with the nucleus itself. Because the neutron is an electrically neutral particle, it is deeply penetrating, and is therefore more able to probe the bulk material. Consequently, it enables the use of a wide range of sample environments that are difficult to use with synchrotron x-ray sources. It also has the advantage that the cross sections for interaction do not increase with atomic number as they do with radiation from a synchrotron x-ray source. Thus neutrons can be used to analyse materials with low atomic numbers like proteins and surfactants. This can be done at synchrotron sources but very high intensities are needed which may cause the structures to change. Moreover, the nucleus provides a very short range, isotropic potential varying randomly from isotope to isotope, making it possible to tune the nuclear scattering contrast to suit the experiment:

The neutron has an additional advantage over the x-ray photon in the study of condensed matter. It readily interacts with internal magnetic fields in the sample. In fact, the strength of the magnetic scattering signal is often very similar to that of the nuclear scattering signal in many materials, which allows the simultaneous exploration of both nuclear and magnetic structure. Because the neutron scattering amplitude can be measured in absolute units, both the structural and magnetic properties as measured by neutrons can be

compared quantitatively with the results of other characterisation techniques.

See also

- Neutron diffraction
- Small angle neutron scattering
- Neutron Reflectometry
- Inelastic neutron scattering

  - neutron triple-axis spectrometry
  - neutron time-of-flight scattering
  - neutron backscattering
  - neutron spin echo
  - neutron resonance spin echo
- Neutron scattering facilities

External links

- Neutron Scattering - A primer [1] (LANL-hosted black and white version [2]) - An introductory article written by Roger Pynn (Los Alamos National Laboratory)

References

[1] http://knocknick.files.wordpress.com/2008/04/neutrons-a-primer-by-rogen-pynn.pdf

[2] http://library.lanl.gov/cgi-bin/getfile?00326651.pdf

Synchrotron

A **synchrotron** is a particular type of cyclic particle accelerator in which the magnetic field (to turn the particles so they circulate) and the electric field (to accelerate the particles) are carefully synchronized with the travelling particle beam. The proton synchrotron was originally conceived by Sir Marcus Oliphant[1] . The honour of the first to publish the idea belongs to Vladimir Veksler, and the first electron synchrotron was constructed by Oliphant's supervisor Edwin McMillan.

Here, the synchrotron is the circular track, off which the beamlines branch.
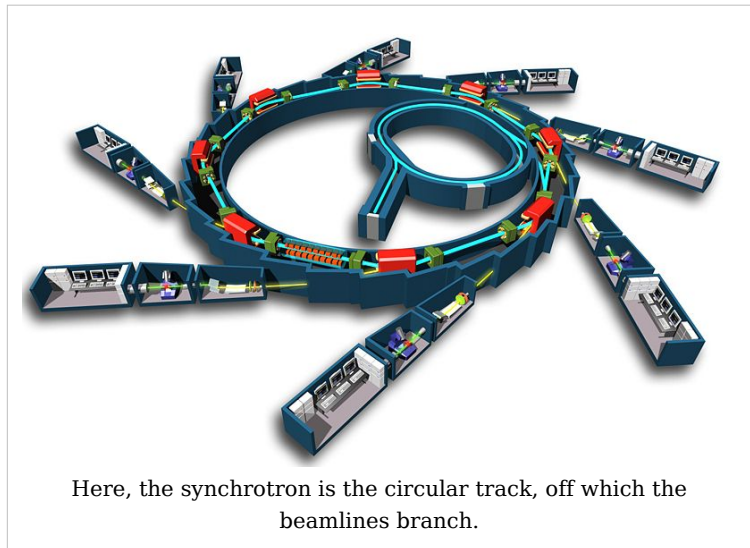
Characteristics

While a cyclotron uses a constant magnetic field and a constant-frequency applied electric field (one of these is varied in the synchrocyclotron), both of these fields are varied in the synchrotron. By increasing these parameters appropriately as the particles gain energy, their path can be held constant as they are accelerated. This allows the vacuum chamber for the particles to be a large thin torus. In reality it is easier to use some straight sections between the bending magnets and some bent sections within the magnets giving the torus the shape of a round-cornered polygon. A path of large effective radius may thus be constructed using simple straight and curved pipe segments, unlike the disc-shaped chamber of the cyclotron type devices. The shape also allows and requires the use of multiple magnets to bend the particle beams. Straight sections are required at spacings around a ring for both radiofrequency cavities, and in third generation light sources allow space for insertion devices such as wigglers and undulators.

The maximum energy that a cyclic accelerator can impart is typically limited by the strength of the magnetic field(s) and the minimum radius (maximum curvature) of the particle path.

In a cyclotron the maximum radius is quite limited as the particles start at the center and spiral outward, thus the entire path must be a self-supporting disc-shaped evacuated chamber. Since the radius is limited, the power of the machine becomes limited by the strength of the magnetic field. In the case of an ordinary electromagnet the

The interior of the Australian Synchrotron facility. Dominating the image is the storage ring, showing the optical diagnostic beamline at front right. In the middle of the storage ring is the booster synchrotron and linac

field strength is limited by the saturation of the core (when all magnetic domains are aligned the field may not be further increased to any practical extent). The arrangement of the single pair of magnets the full width of the device also limits the economic size of the device.

Synchrotrons overcome these limitations, using a narrow beam pipe which can be surrounded by much smaller and more tightly focusing magnets. The ability of this device to accelerate particles is limited by the fact that the particles must be charged to be accelerated at all, but charged particles under acceleration emit photons (light), thereby losing energy. The limiting beam energy is reached when the energy lost to the lateral acceleration required to maintain the beam path in a circle equals the energy added each cycle. More powerful accelerators are built by using large radius paths and by using more numerous and more powerful microwave cavities to accelerate the particle beam between corners. Lighter particles (such as electrons) lose a larger fraction of their energy when turning. Practically speaking, the energy of electron/positron accelerators is limited by this radiation loss, while it does not play a significant role in the dynamics of proton or ion accelerators. The energy of those is limited strictly by the strength of magnets and by the cost.

Design and operation

Particles are injected into the main ring at substantial energies by either a linear accelerator or by an intermediate synchrotron which is in turn fed by a linear accelerator. The "linac" is in turn fed by particles accelerated to intermediate energy by a simple high voltage power supply, typically a Cockcroft-Walton generator.

Starting from an appropriate initial value determined by the injection velocity the magnetic field is then increased. The particles pass through an electrostatic accelerator driven by a high alternating voltage. At particle speeds not close to the speed of light the frequency of the accelerating voltage can be made roughly proportional to the current in the bending magnets. A finer control of the frequency is performed by a servo loop which responds to the detection of the passing of the traveling group of particles. At particle speeds approaching light speed the frequency becomes more nearly constant, while the current in the bending magnets continues to increase. The maximum energy that can be applied to the particles (for a given ring size and magnet count) is determined by the saturation of the cores of the bending magnets (the point at which increasing current does not produce additional magnetic field). One way to obtain additional power is to make the torus larger and add additional bending magnets. This allows the amount of particle redirection at saturation to be less and so the particles can be more energetic. Another means of obtaining higher power is to use superconducting magnets, these not being limited by core saturation.

Large synchrotrons

One of the early large synchrotrons, now retired, is the Bevatron, constructed in 1950 at the Lawrence Berkeley Laboratory. The name of this proton accelerator comes from its power, in the range of 6.3 GeV (then called BeV for billion electron volts; the name predates the adoption of the SI prefix giga-). A number of heavy elements, unseen in the natural world, were first created with this machine. This site is also the location of one

Modern industrial-scale synchrotrons can be very large (here, Soleil near Paris)

of the first large bubble chambers used to examine the results of the atomic collisions produced here.

Another early large synchrotron is the Cosmotron built at Brookhaven National Laboratory which reached 3.3 GeV in 1953.[2]

Until August 2008, the highest energy synchrotron in the world was the Tevatron, at the Fermi National Accelerator Laboratory, in the United States. It accelerates protons and antiprotons to slightly less than 1 TeV of kinetic energy and collides them together. The Large Hadron Collider (LHC), which has been built at the European Laboratory for High Energy Physics (CERN), has roughly seven times this energy. It is housed in the 27 km

tunnel which formerly housed the Large Electron Positron (LEP) collider, so it will maintain the claim as the largest scientific device ever built. The LHC will also accelerate heavy ions (such as lead) up to an energy of 1.15 PeV.

The largest device of this type seriously proposed was the Superconducting Super Collider (SSC), which was to be built in the United States. This design, like others, used superconducting magnets which allow more intense magnetic fields to be created without the limitations of core saturation. While construction was begun, the project was cancelled in 1994, citing excessive budget overruns — this was due to naïve cost estimation and economic management issues rather than any basic engineering flaws. It can also be argued that the end of the Cold War resulted in a change of scientific funding priorities that contributed to its ultimate cancellation.

While there is still potential for yet more powerful proton and heavy particle cyclic accelerators, it appears that the next step up in electron beam energy must avoid losses due to synchrotron radiation. This will require a return to the linear accelerator, but with devices significantly longer than those currently in use. There is at present a major effort to design and build the International Linear Collider (ILC), which will consist of two opposing linear accelerators, one for electrons and one for positrons. These will collide at a total center of mass energy of 0.5 TeV.

However, synchrotron radiation also has a wide range of applications (see synchrotron light) and many 2nd and 3rd generation synchrotrons have been built especially to harness it. The largest of those 3rd generation synchrotron light sources are the European Synchrotron Radiation Facility (ESRF) in Grenoble, France, the Advanced Photon Source (APS) near Chicago, USA, and SPring-8 in Japan, accelerating electrons up to 6, 7 and 8 GeV, respectively.

Synchrotrons which are useful for cutting edge research are large machines, costing tens or hundreds of millions of dollars to construct, and each beamline (there may be 20 to 50 at a large synchrotron) costs another two or three million dollars on average. These installations are mostly built by the science funding agencies of governments of developed countries, or by collaborations between several countries in a region, and operated as infrastructure facilities available to scientists from universities and research organisations throughout the country, region, or world. More compact models, however, have been developed, such as the Compact Light Source.

List of installations

Synchrotron	Location & Country	Energy (GeV)	Circumference (m)	Commissioned	Decommissioned
Advanced Photon Source (APS)	Argonne National Laboratory, USA	7.0	1104	1995	
ISIS	Rutherford Appleton Laboratory, UK	0.8	163	1985	
Australian Synchrotron	Melbourne, Australia	3	216	2006	
LNLS	Campinas, Brazil	1.37	93.2	1997	
SESAME	Allaan, Jordan	2.5	125	Under Design	

Bevatron	Lawrence Berkeley Laboratory, USA	6	114	1954	1993
Advanced Light Source	Lawrence Berkeley Laboratory, USA	1.9	196.8	1993	
Cosmotron	Brookhaven National Laboratory, USA	3	72	1953	1968
Nimrod	Rutherford Appleton Laboratory, UK	7		1957	1978
Alternating Gradient Synchrotron (AGS)	Brookhaven National Laboratory, USA	33	800	1960	
Stanford Synchrotron Radiation Lightsource	SLAC National Accelerator Laboratory, USA	3	234	1973	
Cornell High Energy Synchrotron Source (CHESS)	Cornell University, USA	5.5	768	1979	
Soleil	Paris, France	3	354	2006	
Shanghai Synchrotron Radiation Facility (SSRF)	Shanghai, China	3.5	432	2007	
Proton Synchrotron	CERN, Switzerland	28	628.3	1959	
Tevatron	Fermi National Accelerator Laboratory, USA	1000	6300	1983	
Swiss Light Source	Paul Scherrer Institute, Switzerland	2.8	288	2001	
Large Hadron Collider (LHC)	CERN, Switzerland	7000	26659	2008	
BESSY II	Helmholtz-Zentrum Berlin in Berlin, Germany	1.7	240	1998	
European Synchrotron Radiation Facility (ESRF)	Grenoble, France	6	844	1988	
MAX-I	MAX-lab, Sweden	0.55	30	1986	
MAX-II	MAX-lab, Sweden	1.5	90	1997	
MAX-III	MAX-lab, Sweden	0.7	36	2008	
ELETTRA	Trieste, Italy	2-2.4	260	1993	
Diamond Light Source	Oxfordshire, UK	3	561.6	2002	
DORIS III	DESY, Germany	4.5	289	1980	
PETRA II	DESY, Germany	12	2304	1995	2007
Canadian Light Source	University of Saskatchewan, Canada	2.9	171	2002	

SPring-8	RIKEN, Japan	8	1436	1997	
Taiwanese National Synchrotron Radiation Research Center	Hsinchu Science Park, Taiwan	3.3	518.4	2008	
Synchrotron Light Research Institute (SLRI)	Nakhon Ratchasima, Thailand	1.2	81.4	2004	
Indus 1	Raja Ramanna Centre for Advanced Technology, Indore, India	0.45		1999	
Indus 2	Raja Ramanna Centre for Advanced Technology, Indore, India	2.5	36	2005	
Synchrophasotron	JINR, Dubna, USSR	10	180	1957	2005
U-70	IHEP, Protvino, USSR	70		1967	
CAMD	LSU, Louisiana, US	1.5	-	-	

- Note: in the case of colliders, the quoted power is often double what is shown here. The above table shows the power of one beam but if two opposing beams collide head on, the effective power is doubled.

Applications

- Life sciences: protein and large molecule crystallography
- Drug discovery and research
- "Burning" computer chip designs into metal wafers
- Studying molecule shapes and protein crystals
- Analyzing chemicals to determine their composition
- Observing the reaction of living cells to drugs
- Inorganic material crystallography and microanalysis
- Fluorescence studies
- Semiconductor material analysis and structural studies
- Geological material analysis
- Medical imaging
- Proton therapy to treat some forms of cancer

See also

- List of synchrotron radiation facilities
- Synchrotron X-ray tomographic microscopy
- Energy amplifier
- Superconducting Radio Frequency

References

[1] Nature 407, 468 (28 September 2000) (http://www.nature.com/nature/journal/v407/n6803/full/407468a0.html).
[2] The Cosmotron (http://www.bnl.gov/bnlweb/history/cosmotron.asp)

External links

- Australian Synchrotron (http://www.synchrotron.org.au)
- Diamond UK Synchrotron (http://www.diamond.ac.uk)
- Lightsources.org (http://www.lightsources.org/cms/)
- CERN Large Hadron Collider (http://lhc-new-homepage.web.cern.ch/lhc-new-homepage)
- Synchrotron Light Sources of the World (http://www-als.lbl.gov/als/synchrotron_sources.html)
- A Miniature Synchrotron: (http://www.technologyreview.com/Biotech/20149/) room-size synchrotron offers scientists a new way to perform high-quality x-ray experiments in their own labs, *Technology Review*, February 04, 2008
- Brazilian Synchrotron Light Laboratory (http://www.lnls.br/lnls/cgi/cgilua.exe/sys/start.htm?UserActiveTemplate=lnls_2007_english&tpl=home)
- Podcast interview (http://omegataupodcast.net/2009/03/28/11-synchrotron-radiation-science-at-esrf/) with a scientist at the European Synchrotron Radiation Facility

ISIS neutron source

ISIS is a world leading pulsed neutron and muon source. It is situated at the Rutherford Appleton Laboratory in Oxfordshire, United Kingdom and is part of the Science and Technology Facilities Council . It uses the techniques muon spectroscopy and neutron scattering to probe the structure and dynamics of condensed matter on a microscopic scale ranging from the subatomic to the macromolecular.

Hundreds of experiments are performed annually at ISIS by visiting researchers from around the world, in diverse science areas including physics, chemistry, materials engineering, earth sciences, biology and archaeology.

ISIS Logo

ISIS experimental hall for Target Station 1

Neutrons and muons

Neutrons are uncharged constituents of atoms and penetrate materials well, deflecting only from the nuclei of atoms. The statistical accumulation of deflected neutrons at different positions beyond the sample can be used to find the structure of a material, and the loss or gain of energy by neutrons can reveal the dynamic behaviour of parts of a sample, for example diffusive processes in solids. At ISIS the neutrons are created by accelerating 'bunches' of protons in a synchrotron, then colliding these with a heavy tantalum metal target, under a constant cooling load to dissipate the heat from the 160 kW proton beam. The tantulum atoms slough off neutrons, and these are channelled through guides, or beamlines, to about 20 instruments, individually optimised for the study of different types of matter. The target station and most of the instruments are set in a large hall. The penetrating neutrons are a dangerous form of radiation so the target and beamlines are heavily shielded with concrete.

ISIS produces muons by colliding a fraction of the proton beam with a graphite target, producing pions which decay rapidly into muons, delivered in a spin-polarised beam to sample stations.

Science at ISIS

ISIS is administered and operated by the Science and Technology Facilities Council (previously CCLRC). Experimental time is open to academic users from funding countries and is applied for through a twice-yearly 'call for proposals'. Research allocation, or 'beam-time', is allotted to

Another view of the ISIS experimental hall for Target Station 1

applicants via a peer-review process. Users and their parent institutions do not pay for the running costs of the facility, which are as much as £11,000 per instrument per day. Their transport and living costs are also refunded whilst carrying out the experiment. Most users stay in Ridgeway House, a hotel near the site, or at Cosener's House, an STFC-run conference centre in Abingdon. Over 600 experiments by 1600 users are completed every year.

A large number of support staff operate the facility, aid users, and carry out research, the control room is staffed 24 hours a day, every day of the year. Instrument scientists oversee the running of each instrument and liaise with users, and other divisions provide sample environment, data analysis and computing expertise, maintain the accelerator, and run education programmes.

Among the important and pioneering work carried out was the discovery of the structure of high-temperature superconductors and the solid phase of buckminster-fullerene.

Construction for a second target station started in 2003, and the first neutrons were delivered to the target on December 14 2007[1] . It will use low-energy neutrons to study soft condensed matter, biological systems, advanced composites and nanomaterials. To supply the extra protons for this, the accelerator is being upgraded.

History and background of ISIS

The source was approved in 1977 for the RAL site on the Harwell campus and recycled components from earlier UK science programmes including the accelerator hall which had previously been occupied by the Nimrod accelerator. The first beam was produced in 1984, and the facility was formally opened by the then Prime Minister Margaret Thatcher in October 1985.[2]

The name ISIS is not an acronym: it refers to the Ancient Egyptian goddess and the local name for the River Thames. The name was selected for the official opening of the facility in 1985, prior to this it was known as the SNS, or Spallation Neutron Source. The name was considered appropriate as Isis was a goddess who could restore life to the dead, and ISIS made use of equipment previously constructed for the Nimrod and Nina accelerators[3] .

External links

- ISIS facility [22]
- ISIS Second Target Station [4]
- The Science and Technology Facilities Council [5]

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[1] ISIS Second Target Station Project (http://ts-2.isis.rl.ac.uk/)

[2] Linacs at the Rutherford Appleton Laboratory (http://epubs.cclrc.ac.uk/bitstream/692/linacplahistory.pdf)

[3] Explanation of the name of ISIS (http://www.isis.rl.ac.uk/aboutIsis/index.htm)

[4] http://ts-2.isis.rl.ac.uk/

[5] http://www.stfc.ac.uk

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