Division of Computer Research and Technology

Annual Report of Program Activities
October 1, 1978 through September 30, 1979

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DIRECTOR'S SUMMARY

The success of DCRT in FY 1979 stands forth in the details of this annual report as a tribute to three factors:

1. Fundamentally sound principles behind the NIH decision to establish a "computer" division in 1964;

2. Continuing high quality of work by members of the DCRT laboratories and branches across discipline and organizational lines;

3. Effective long-term working relationships between DCRT staff and scientists and administrators throughout NIH.

The Director, NIH, established DCRT in 1964 to embody certain principles set forth by the report in 1963 from an NIH study of computing and data processing at NIH. These concepts included:

- A central NIH resource to conduct research and technical development in computing as well as to provide computing services for NIH.

- A multidisciplinary organization with several distinct laboratories and branches--combining expertise in mathematics, statistics, electronic engineering, and a variety of biomedical disciplines--as a way to reduce recognized barriers in making a powerful emerging computing technology an integral part of the NIH programs.

- A division co-equal within the NIH structure to carry the primary responsibility for this new approach to computing at NIH.

Two Illustrative Stories

The subsequent history of DCRT and computing at NIH has illustrated the validity of these basic ideas. The following two stories are examples of long term collaborative efforts possible only under conditions designed to foster multidisciplinary and multigroup interaction among DCRT staff and NIH scientists.

The first story began in 1969 when the DCRT Laboratory of Applied Studies (LAS) conceived a project to apply computer processing techniques to x-ray-like images recorded by so-called "gamma cameras" from minute amounts of radioactive materials administered by the Nuclear Medicine Department of the NIH Clinical Center. The DCRT Computer Systems Laboratory (CSL) joined LAS to specify the appropriate camera-computer system since none was available commercially. The first five years of this project went largely into developing hardware and software systems and mathematical techniques and proving their feasibility.

Then quite rapidly over 15 months in 1975-76, basic techniques were applied by members of the Nuclear Medicine Department and the Cardiology Branch to exercise tests in patients with coronary artery disease, demonstrating a valuable new tool for diagnosis and treatment. Publication of their results triggered a nationwide recognition of the value of the technique. It is now commercially available from several companies and is a routine procedure in major hospitals (e.g., N. Eng. J. Med. 301:94, 1979).

Meanwhile, the collaboration between DCRT and the Nuclear Medicine Branch also has provided NIH with unexcelled facilities for computer processing of dynamic images from the heart, lungs, kidneys and other organs. One of the current collaborative projects in this lineage combines expertise from the Pulmonary and Clinical Hematology Branches, NHLBI, with DCRT and Clinical Center staff in studies of lung disease and its effects on pulmonary functions.

The second story began in 1968 with a decision by the DCRT Division Director to develop a computer based dynamic display for chemical structures. Initial development of the hardware and software systems again took several years in a collaborative project between members of the Computer Center Branch (CCB) and the Heuristics Laboratory (HL) in DCRT. (HL was abolished in 1974 as the result of a DCRT reorganization caused by loss of positions during the 1970-74 Federal employment retrenchments.)

A number of versatile techniques were exploited in the early and mid 1970s to provide black and white "skeletal" models of macro molecules used in projects by scientists in the DCRT Physical Sciences Laboratory (PSL) and the Laboratory of Molecular Biology in NIAMDD.

The ability to produce stereo images and moving pictures of molecules was particularly useful. An atlas of macromolecular structures on microfiche made inexpensive stereo views of scores of large molecules available to scientists throughout the world, who did not have computer systems comparable to the one available to NIH scientists.

In 1978 the DCRT armamentarium of graphic techniques was expanded with new hardware and software to create "space filling" full color models from the extensive library of macromolecular coordinates compiled by DCRT staff in conjunction with biochemists and x-ray crystallographers around the world.

In FY79 the new system was used by the staff of other DCRT and NIH laboratories for a widening array of chemical and medical images with NIDR, NIAMDD, NINCDS, NHLBI, NCI and the Clinical Center.

Two Later Developments

This pattern of long-term investment in collaboration to develop and exploit a set of basic technical tools appears in two other projects that are now beginning to show promise:

- Data base management expertise developed over the last five years by CCB and the DCRT Data Management Branch (DMB) has provided the basis for collaboration with NIH administrative management divisions. Projects to improve NIH material management and accounting systems are well underway.

- A clinical information data base technology was developed over the last six years by DMB's working with the Clinical Center's Office of Clinical and Management Systems. This has been used by 170 NIH clinical scientists to retrieve specific kinds of data from some 15 million test results recorded by the Clinical Laboratories of the Clinical Center. During FY79 the Office of the Director in the Clinical Center has moved to use the technology to improve medical records in support of patient care by all NIH clinical services; collaboration has begun with the DCRT Laboratory of Statistical and Mathematical Methodology (LSM) to provide improved facilities for building and analyzing subsets of clinical research data.

The Pervasive Pattern

Over the years multidisciplinary collaboration among members of the DCRT has also been an essential part of many "short term" projects in support of or in collaboration with members of other NIH Institutes and Divisions.

A survey this year disclosed 50 projects in each of which members of two or more of the six DCRT Laboratories and Branches worked together to provide mutually supportive scientific, mathematical, engineering, or computing expertise. Indeed this mutual support is an accepted part of day-to-day activities. It goes without notice in many annual reports of the DCRT staff in much the same way that much of the cross-supporting activity among scientists in the NIH Institutes is taken for granted.

Access to Computing Throughout NIH

There is another equally important measure of the validity of the concepts and principles built into the DCRT. This is the computing done independently by NIH staff using the facilities provided by the DCRT.

In FY79 there were over 3000 registered NIH users of the computer center designed and operated by CCB. A study of the patterns of use in FY78 indicates that about half this $10 million expenditure in FY79 will have supported NIH intramural biomedical and biometric programs. The other

half is distributed across the extramural, collaborative and administrative management programs of NIH.

Indeed, this very mixture of science and administration at NIH was recognized as a unique circumstance by the 1963 recommendation to establish a separate division for computing at NIH. It proved to be a driving force behind the development by CCB of a balanced "Computer Utility" that combines facilities for scientific computing and administrative data processing. Programs written by CCB systems programmers link these distinct components into a single functional system, the total power of which was available in FY79 through 1800 remote terminals to all users in their diverse working environments, scientific and administrative.

Central Support for Independent Users

It is well known that even the best computer systems are necessary but not sufficient to produce successful computing, particularly for people whose primary work is not computers. Some of the other essential ingredients are provided at NIH by additional expertise within DCRT: in DMB, in LSM, and in the User Services and Assistance Section of CCB.

DMB and LSM have developed or adapted a set of data management and analysis tools that support the use of the NIH Computer Utility throughout NIH. These tools are packages of programs that can be used directly for many computer applications. DMB and LSM teach the use of these packages in courses given twice each year. They provide advice for users and technical support for the packages throughout the year. In FY79 these programs on the NIH computers were used hundreds of thousands of times.

The User Services and Assistance Section provides support for programmers and people who want to learn to program. In FY79 they organized or conducted 64 computer training courses and seminars for 1300 applicants. The section handled almost 20,000 calls or visits for assistance during the year and provided over 80,000 technical manuals and other documents to guide programmers and other users of the NIH central computing facilities.

Support for Computing Outside DCRT

The DCRT role in the successful application of computing throughout NIH goes beyond computing at the NIH Computer Center. The 1963 plan saw the evolution of smaller computer systems, particularly in the laboratories and clinics of NIH. In FY79, as in previous years, CSL worked on more than two dozen projects to put minicomputers or microcomputers to work where they were better suited to particular scientific needs than a central computing facility.

In addition to the computing in which DCRT has a role, NIH makes use of outside sources for computing resources in both intramural and collaborative programs. In FY79 the DCRT ADP Policy Office reviewed over 450

procurement actions for computer equipment and services throughout NIH. Many of these reviews called on expertise in the DCRT laboratories and branches for advice.

Another area of support centers around access to books, journals, and reports that provide insight to what has been done in computer science and technology and its applications to biomedical science. The DCRT Library, an independent "full service" library which began as support for the diverse needs of the DCRT staff, now has more active registered users from the NIH staff outside DCRT than from the DCRT itself.

Outside NIH

The success of computing activities at NIH continued to attract visitors and inquiries from across the country and quite literally around the world. In FY79 they came from every continent (except Antarctica), from the USSR, Eastern Europe, and Mainland China, as well as more accessible areas. Recognition within the Federal government itself came in the form of requests for DCRT staff to serve as advisors, consultants, and collaborators with other agencies and for access to the NIH computing facilites.

Activities in the Federal Sphere

The desire of other Federal agencies to benefit from the NIH accomplishments in computing continues to be a mixed blessing to DCRT. In FY79 the General Services Administration formally recognized the general purpose NIH computer center facility provided by CCB as a Federal Data Processing Center for Biomedical and Statistical Computation and the CCB Chief, Mr. Joseph Naughton, received the "Man of the Year" award from the Federal Interagency Committee on Automatic Data Processing.

Although many other agencies wished to use NIH facilities, DCRT had to continue its policy, established in 1974, restricting outside users, virtually denying access to new agency applications for use of the facilities. Despite these limitations, DCRT found itself embroiled in the efforts of private computer service firms to obtain business from current users of the NIH computing facilities. These efforts included Congressional Inquiries and a spate of Freedom of Information requests.

Computing for NIH Science

Notwithstanding the facts noted above (half the NIH computer center expenditures in direct support of scientific activities and the vast bulk of CSL work on computer systems for NIH laboratories and clinics) there has been concern about computing resources for science at NIH.

Part of this concern reflects a growing recognition that computing is indeed essential for much of biomedical science. The situation in some parts of biomedical science has reached the stage stated by Weisskopf in his recent article on "Contemporary Frontiers in Physics" (Science 203: 240, 1979): "Modern physics without modern computers is

unthinkable." As Weisskopf noted, "There is a special reason why new discoveries were made... namely the exuberant growth of new instrumentation and the maturing of previous innovations which become ready for full exploitation. A partial list of examples includes lasers... and, most important, computers."

But another part reflects the belief that any large expenditures of funds deserve examination. This view led the NIH Deputy Director for Science to create, in FY78, an NIH Advisory Committee on Computer Usage. FY79 was the first full year of its activity. It took a strong position to insure that the new Federal Data Processing Center role for NIH did not cause NIH scientific use of computers to take second place.

Procurement of Improved Computing Machinery

DCRT made some progress on the perennial issue of procuring replacement for the aging hardware in the NIH computer utility. An additional year of work with the General Services Administration in FY79 produced Requests for Proposals to replace the existing DEC System 10 and IBM 370 computers. It is impossible at this point to predict what systems will be proposed by vendors, how much time will be needed for the rest of the selection and procurement process, and what problems will be encountered in installing the new equipment as an integral part of the NIH computing activities. It is clear, however, that newer computers already in production and installed elsewhere in the nation can provide a significant increase in computing capacity at less cost to NIH users.

Restricted Employment Levels

Another perennial issue not forseen in the original plans for DCRT is the recurring cuts in DCRT staff. The 1963 report predicted some 600 employees in the Division by 1968. In fact the allocation of positions for DCRT peaked in FY 1969 at 316 and has followed an almost monotonic decline ever since. FY79 brought a new loss of 16 positions from those budgeted for the year.

The cumulative effect over 10 years has been to reduce the original 316 positions to 235. Other organizations have been willing to transfer some positions to DCRT to support activities of importance to them, primarily the service functions. But these gifts have left the Division with a hidden "nutritional" deficiency. The overall DCRT staffing level masks starvation in many of the multidisciplinary areas essential for computing excellence at NIH.

The basic principles stated in 1963 still apply. But the emergence of new opportunities in areas such as non-numeric computing and image processing will require the addition of some new expertise. There will be a need for young scientists to bridge the interface between computer expertise and the science of new application areas. How DCRT can modify its programs to adjust to these circumstances is not yet clear. Renewal is not easily accomplished in periods of retrenchment.

Another Possible Problem

An additional small cloud over the future plans of DCRT is the congressionally mandated review of all NIH activities under OMB Circular A-76. The history of DCRT and computing at NIH shows that all parts of DCRT have functioned as an integral and inseparable part of the NIH core activities. It seems inconceivable that parts of the Division could be put out on bid as a separate "commercial or industrial activity" without irreparable harm to the intricate web of functions that have developed in computing at NIH over the last decade. But the word that NIH intramural scientific research itself faces this very A-76 review makes the inconceivable somewhat less unthinkable, but no less threatening and potentially destructive.

Arnold W. Pratt, M.D., Director
Division of Computer Research
and Technology

OFFICE OF THE DIRECTOR

The first month of FY79, DCRT took part in an NIH Science Writer's Seminar on Computer Medicine. Conversing before the program were (l. to r.) Dr. Thomas Lewis of the Clinical Center with DCRT Director Dr. Arnold Pratt and two of his staff, Dr. Judith Prewitt and Mr. Martin Epstein.

OFFICE OF SCIENTIFIC AND TECHNICAL COMMUNICATIONS

William C. Mohler, M.D.
Chief

I. SUMMARY

Function and Scope

The DCRT office of Scientific and Technical Communications, under the direction of the Associate Director, DCRT, includes:

- The DCRT Information Office, which serves as the focus for providing the NIH community and the general public with information about DCRT's activities and its relationship to biomedical research. The office handles a wide range of inquiries, produces print and audio-visual communications, coordinates special events, and provides advice, assistance and educational resources for DCRT staff.

- The DCRT Library, which maintains a special collection in computer science and mathematics, statistics, engineering, information science, and management. The library directly supports DCRT activities and is a resource for other NIH staff. It also functions as an integral part of the local Washington area network of special libraries.

- Scientists assigned to this office, working on research and development projects in biomedical data bases, image processing, and decision analysis.

Highlights of FY79 Activities

The DCRT Information Office got a new Information Officer, Patricia Orsino Miller, in December. She and Public Information Specialist Mary Hodges, the other member of this small office, undertook a widening set of activities during the year.

In addition to over 5,000 varied public inquiries about DCRT and computing in biomedical activities, a minor flood of Freedom of Information requests arrived during the last half of this year. Many of these and two Congressional Inquiries through the Office of Management and Budget appeared to arise from the desire of a private computer service organization to recruit business among users of the NIH Computer Center.

A new portable exhibit unit, designed by the office, was first used in the spring in support of a DCRT Computer Systems Laboratory demonstration at the President's Conference on Employment for the Handicapped. A few weeks later it proved its "modular, multipurpose" capability by appearing with new graphics at the ceremonies establishing the general purpose facility of the NIH Computer Center as a Federal Data Processing Center for Biomedical and Statistical Computing.

These two events, arranged by the Information Office, were examples of a growing interest outside of NIH in DCRT activities. In addition to preparing news articles for local papers, the office responded to requests from IEEE Spectrum and Smithsonian magazines and a Canadian TV station for feature stories, still photography, and 16mm footage describing DCRT work.

But most of the work of the office during FY79 continued to focus on information for NIH scientists and others interested in what DCRT does and how it can help their work. This meant the hidden labor of revising, reprinting, and distributing some 3,000 copies of several brochures describing the activities of the division and its laboratories and branches. It included arranging and helping other DCRT staff give tours and talks for groups who came to the DCRT facilities and presentations about the results of DCRT projects. The office produced a simple building directory for visitors that can be revised easily over the coming years as renovations cause relocation of activities in the Building 12A/B complex.

To help the division staff prepare and present their own direct personal communications, the office introduced a new set of activities as part of its longer range DCRT information program. It arranged two staff training seminars in effective speaking techniques and use of visual aids and it produced two sound-on-slide shows as prototypes for presentations that could be tailored to the needs of particular groups.

During FY79, the Information Officer served on the NIH Information Officer's Training Committee, was active in the National Association of Government Communicators and was elected vice-president of Women in Communications, Inc., a national organization for journalism, broadcasting, public relations, and communications professionals.

The DCRT Library operations increased in volume during FY79. The Librarian, Ellen Chu, and the library technician, Jill Lindau, handled more acquisitions, circulation of books, and on-line information searches for more registered users than in FY78.

The increased workload with no increase in staff reflects judicious use of automation. A national cooperative network, OCLC, helped identify, locate, buy, classify, catalog, and borrow books and a new automated "circulation system" went into active use in March. The circulation system, developed by the Library and DCRT Data Management Branch, assures more accurate records of loaned materials. It provides better information on the status and location of books and documents on loan and generates a wide assortment of useful messages and reports for library operations.

As part of the work in coding items for the masterfile of the circulation system, the library staff reviewed and reclassified the book collection to fit changes and expansions that have occurred in the Library of Congress classification system since the Library opened over a decade ago. Part-time and temporary employees helped with the massive manual task of typing in entries for the master files, putting new labels on books, reshelving the books according to the new call numbers, and affixing small printed labels to about 20,000 catalog cards.

Addition of an extra 230 feet of shelving and transfer of some bound journals to microforms reduced crowding on the shelves. A new Minolta 450 reader-printer, purchased to handle the variety of these microform formats, provided an unexpected benefit for editing some 16mm film describing work in the Computer Center Branch.

The number of on-line bibliographic searches increased over 50% this year. MEDLINE and Computer and Control Abstracts were the most heavily used of over 80 data bases now directly searchable at the Library's on-line terminal.

The striking change in the pattern of interlibrary loans continued. In earlier years the Library borrowed more than it lent. Last year it broke even. In FY79 the requests from other libraries to DCRT were almost twice the requests DCRT made to others. This increase is due to the quality of the DCRT Library collection and the service it provides and to the active participation of the Library and Librarian in a number of formal organizations:

- The Interlibrary Users Association of the Washington-Baltimore Area
- The Metropolitan Washington Library Council
- FEDLINK (a Federal Library consortium)
- The national OCLC library users network.

The Scientific Staff pursued the level of work established in previous years. Dr. Judith Prewitt was again very active outside of NIH organizing meetings, working groups, and collaborative projects. She continued work with the National Cancer Institute staff on their Diagnostic Radiology and Cytology Automation projects. Dr. Shun Chung Wu extended his work on the development of computer algorithms for applications to image processing in cytology.

Martin Epstein expanded the documentation of his MEDINQUIRY System and some of its uses on the melanoma data base, and he collaborated with several scientists outside NIH in developing plans for further applications of the system.

Dr. William Mohler again organized the NIH clinical elective on Computers in Clinical Medicine and worked with the Deputy Director and the Associate Director of the NIH Clinical Center on projects to use the DCRT Clinical Information Utility in condensing medical records, to evaluate the Clinical Center's Medical Information System and to explore data analysis facilities for clinical research.

Future Plans

The activities of this office will continue the major lines followed in FY79 and previous years with the following emphases:

The Information Office plans to:

- update gradually the content and upgrade the format of its existing information publications and add others for complete coverage of DCRT activities

- begin a program to monitor and evaluate the effectiveness of the Division's present information program among the NIH Scientific and Administrative staff

- complete and extend its computer-based index of all DCRT scientific papers to provide retrieval by author, topic, date, and organizational component within DCRT.

The DCRT Library plans to refine the design and use of its circulation system with an emphasis on statistical reports to aid in decisions about modifying the library's collection and services to its users. To prepare for the impending nationwide change to new Anglo-American cataloging rules, it will study the possible conversions of subject headings and authority files.

Plans for the projects of the scientific staff will emphasize some efforts toward greater application of the methods developed to date for selected biomedical applications in order to evaluate this utility.

II. PROJECTS

(The FY79 project reports of Dr. Prewitt were delayed this year and are not included in this list.)

1. Natural Language Access to Clinical Data Bases. M.N. Epstein. The objective of this project, begun in FY77, is the development and evaluation of a system that will allow physicians access to medical data through natural language queries to support both patient management and clinical research. The MEDINQUIRY prototype system and melanoma application were documented in FY79. Other applications were discussed with the National Library of Medicine.

2. DCRT Library Circulation System. E. Chu (Library), J. Mahaffey (DMB). This system, started in FY79, maintains files of records covering monographs and documents in the DCRT library collection, users authorized to borrow them, and transactions on the circulation of items from the collection to the users. In 1979 the library completed the files on all existing items and users. The system is now fully active. Work continued on a document index and statistical reports as products of the system.

3. DCRT Information Program Plan. P. O. Miller and W. C. Mohler. The project began in FY77, became dormant in FY78 and revived in FY79 under the new information officer. The preliminary program has five inter-related parts: Communicative Production and Evaluation, Resource Development, Communication Pathway Development, DCRT Staff Education, and Needs Analysis. Activities in FY79 dealt with Communication Production, with some initial seminars for staff education on communication techniques.

4. Computer Algorithms for Cytology. S. C. Wu and J. M. S. Prewitt. This project started in FY78 to develop new basic computer algorithms for boundary finding, object extraction, and measurement of shape and texture features. Work in FY79 resulted in new techniques in several of these areas.

III. PUBLICATIONS

Epstein, M. N., and Walker, D. E.: Natural language access to melanoma data base. Proc. of Second Annual Symposium on Computer Applications in Medical Care, IEEE Computer Society, 1978, pp 320-325.

Mohler, W. C.: Introduction to Representation of Medical Knowledge. Proc. of Second Annual Symposium on Computer Applications in Medical Care, IEEE Computer Society, 1978, pp 364-5.

Prewitt, J. M. S., and Wu, S. C.: An Application of Pattern Recognition to Epithelial Tissues, Proc. of Second Annual Symposium on Computer Applications in Medical Care, 1978, pp 15.

Computers: Tools for the Advancement of Medicine, DHEW Pub. No. (NIH)-79-1039, 28 pp.

Computing Resources of the Division of Computer Research and Technology. 1978, 48 pp.

Division of Computer Research and Technology: Report of Program Activities October 1, 1977 through September 30, 1978, 180 pp.

Physical Sciences Laboratory, DHEW Pub. No. (NIH)79-1925, 12 pp.

Dr. William C. Mohler, DCRT Associate Director, organizing the fifth NIH clinical elective on Computers in Clinical Medicine.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Basic Computer Algorithms for the Applications of Cytology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Shun Chung Wu, Senior Staff Fellow

COOPERATING UNITS (if any)

None

LAB/BRANCH
Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION
DCRT/NIH

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

(1) A decision tree method has been developed to distinguish the internal pixels of an object with a given chain encoded boundary, regardless of the intensities of these pixels are higher or lower than that of background. (2) An objective boundary tracking method has been created to select one out of several isodensity contours. The criterion for selection is based on an optimizing objective function of area, shape and integrated density. (3) Several measures of visual texture, based on the average local intensity, have been generated. Comparison between this texture and the texture based on transition probability matrix has been studied on bladder tissue sections. (4) A concavity finding algorithm for the chain encoded boundary has directly been produced. (5) These algorithms have been applied to the images of bladder cancer nuclei, white blood cells and computerized tomography.

Project Description:

Objectives:

Because of the lack of the sound basic computer algorithm, the percentage of correct diagnosis made by computer in cytology application is lower than that by human expert. Such algorithms should include the methods for the finding of true boundary, extraction of object, various accurate and meaningful measures of the shape and texture features. If the boundary found by computer algorithms is deviated from the true boundary, all subsequent feature measures and classifications will be subjected to errors and mixed with unwanted noises. For a malignant tumor nucleus, the intensities of pixels inside the nucleus can be either higher or lower than that of background. In order to measure the texture of the tumor nucleus, an extraction algorithm is to be developed to distinguish the internal pixels of the nucleus from the outside region. These basic algorithms are necessary for successful cytology diagnosis by using computer technology.

Significance:

The applications of these algorithms to medical images of white blood cells, CT scans and bladder tumor tissue sections indicate that not only the quality of the measured features has been improved but the percentage of correct classification has been increased also. It is very hopeful that the computer can be used to do a faster diagnosis than human expert in the practical applications.

Proposed Course:

At the present time, the decision tree method to extract object can be applied only to the chain encoded boundary without filaments with 8-neighbor connection. This tree method ought to be modified in order to be applied for 4-neighbor chain encoded connection. Also, the boundary found by optimizing objective function and isodensity contours may deviate from the maximal edge pixels in certain circumstances. A new approach by combining both the method of the optimizing objective function and the method of the maximum edge linkage is to be developed.

Publications:

Wu, S.C. and Prewitt, J.M.S.; Deriving Concavities from the Fourier Coefficients and Its Role in Pattern Recognition. Proc. of the 30th Ann. Conf. on Engineering in Medicine and Biology,1977.
Wu, S.C., Prewitt, J.M.S. and Lehman, J.: To Extract a Connected Object of Arbitrary Shape from its Background by Decision Tree Method. IEEE Comp. Soc. Conf. on Pattern Reco. and Image Pro. 1978.
Prewitt, J.M.S. and Wu, S.C.: An Application of Pattern Recognition to Epithelial Tissues. The Second Ann. Symposium on Computer Application in Medical Care. 1978, pp. 15.

OFFICE OF ADP POLICY COORDINATION

Henry J. Juenemann
Chief

I. Summary of Activities

Functions

The Office of ADP Policy Coordination, under the direction of the Assistant Director of the Division, has two closely related functions.

- It serves as a focus for NIH-wide coordination of automatic data processing policy matters.
- It serves as a central NIH point of contact with the Public Health Service, the Department of Health, Education and Welfare, other HEW Agencies, The General Services Administration, and the Office of Management and Budget on policy questions and NIH's participation in policy development.
- The Office also provides advice and assistance concerning internal DCRT operations and coordinates DCRT's ADP policies and activities with those of other agencies.

Scope

The role of the office includes: advising the Director of DCRT and through him the Director of NIH on ADP policy matters; assisting the NIH Division of Management Policy on questions relating to its responsibility for administrative and management computer applications; reviewing and evaluating proposals from NIH B/I/D/O's for ADP and computing related procurements and contracts; directing the development of the annual NIH ADP Plan; representing the NIH in PHS and DHEW policy formulation efforts; working with GSA staff on procurements; coordinating Interagency Agreements with other Federal agencies that

use DCRT facilities; and answering inquiries from scientists and administrators who are confused by the whole process.

Highlights of FY79 Activities

The annual ADP Plan has changed gradually in the last few years to become an expanded version of Exhibits 43A and 43B of budget submissions required by A-11. This year the Plan was a part of the FY81 budget submission and was again coordinated by this office. This management process, involving all B/I/D/O's provides a forward look at projected ADP efforts necessary to support NIH research and research management programs. The submission showed a total of $51,402,000 FY79 ADP related obligations offset by a net of $8 million in receipts from non-HEW Federal Agencies. The projected figures for FY81 were $60 million offset by an estimated $8.1 million. Projected work years rose from 652 in FY79 to 688 in FY81.

One major highlight of the year was the designation of the DCRT central general purpose computer facility as a Federal Data Processing Center. This agreement was signed on May 31, 1979 by representatives of GSA, HEW, PHS and NIH culminating several years of negotiations aimed at recognizing the long record of DCRT's technological leadership in Federal computing and our mutually beneficial participation in the Sharing Program envisioned by the Brooks Law, The agreement was cast in terms assuring that the new role would not disrupt the computing support needed by NIH's own research programs. A second form of recognition was received by NIH when this office's nomination of the Chief of the Computer Center Branch to be Federal "ADP Man of the Year" was accepted on behalf of the whole Federal ADP community by the Interagency Committee for ADP. Mr. Joseph Naughton was accorded that honor on June 12, 1979.

In the process of monitoring the policy implications of NIH's ADP involvements and assuring conformity to existing OMB, GSA and Department regulations, this office reviewed 456 proposals for ADP equipment or services during the period. This is more than half again over the corresponding figure for last year. This office continues to be very fortunate in being able to call on the expertise of the other laboratories and branches of DCRT. During the year they were extremely helpful in insuring that technical merit is able to be a part of the review process.

The major efforts required to reprocure both the 370 and DECSystem 10 facilities continued throughout the year. By the beginning of the fourth quarter, it appeared that we had reached agreement with GSA on a draft of the 370 solicitation to be released to industry for comment. Competitive solicitations for supplying NIH standard 30 and 120 CPS hard copy terminals were successfully completed as was the procurement of Mass Storage Units to augment on-line data storage capabilities.

One major highlight of the year was the designation of the DCRT general purpose computer facility as a Federal Data Processing Center (FDPC). The May 31 event was the culmination of several years of negotiations, largely the effort of DCRT Assistant Director Henry Juenemann (third from left).

PHS Deputy Assistant Secretary for Health Operations Charles Miller, GSA Assistant Commissioner Dr. Robert Coyer, and NIH Director Dr. Donald Fredrickson affixing their signatures. Five officials--representing GSA, HEW, PHS, and NIH--signed the FDPC agreement.

Future Plans

Federal ADP policies and requirements continue to become more and more complex as OMB, GSA, DHEW and PHS become more and more involved. As a result, the Office must spend an increasing portion of its available man-hours in attempting to guide NIH policy in productive directions and in meeting regulatory requirements. The Office will continue its work to spare large numbers of NIH research and research support staff members the task of becoming expert in the many nuances of ADP-related regulations. However, it is anticipated that the two simultaneous full recompetition efforts for both of NIH's main computer systems will consume a significant portion of the resources of this office during the upcoming year and require extensive assistance from OD and CCB Staff.

One of the signers of the agreement, GSA Commissioner Frank Carr, is seated at the table. Another signer, HEW Deputy Assistant Secretary L. David Taylor, addresses officials from the U.S. Congress, NIH, PHS, HEW, OMB, and GSA.

OFFICE OF ADMINISTRATIVE MANAGEMENT

L. Lee Manuel
Chief

SUMMARY

Function

The Office of Administrative Management, under the direction of the Executive Officer, provides administrative, financial and personnel management for the Division's program. The office serves as liaison to these functions with the NIH Office of Administration and other NIH, PHS and other DHEW offices.

Scope and Activities

The office handles the usual range of administrative managerial functions for an NIH research division of almost 300 people. The Financial Management/Project Control Sections maintains 2000 project accounts involving 6400 registered users of the DCRT computer facilities and services. These services total an estimated $26,000,000 in FY 78. Requisitions, contracts, travel, and training documents are processed by the Administrative Services Section and covers a variety of procurements of approximately $20 million. Day to day activities also cover support in areas of space, telephone changes, payroll and other miscellaneous administrative subjects.

Highlights of FY79 Activities

The Personnel Section continued its mandated three year position classification review of all positions and reported several to higher authorities for both downgrading and upgrading. The Civil Service Reform Act required implementing the senior executive service at the DCRT level and new evaluation criteria to cover appraisal of supervisors and managers in the GS-13 through 15 level.

The Financial Management Section was the primary focus for development and coordination of basic materials for the DCRT portion of the NIH Forward Plan, Zero Based Budgetary Workload/Manpower reporting and the normal Federal Budget process.

New requirements mandated by the Secretary, DHEW required intensive efforts by the Administrative staff in the areas of contracting, procurement, travel and consultant services. Most of these requirements called for detailed plans to be prepared and monthly and quarterly reporting requirements were mandated. Also certain delegations of authority were elevated to higher levels. All of these actions tended to increase the amount of "paperwork" required and further slowed the already cumbersome administrative processes. A new EEO effort required an in-depth analysis of the DCRT workforce. The DCRT Administrative Information Retreival System (AIRS) was used to generate our staffing charts this year. This eliminated a lengthy typing chore for the staff.

The Project Control Office ran a pilot survey of NIH users of DCRT services to determine the extent to which these services support major categories of NIH work.

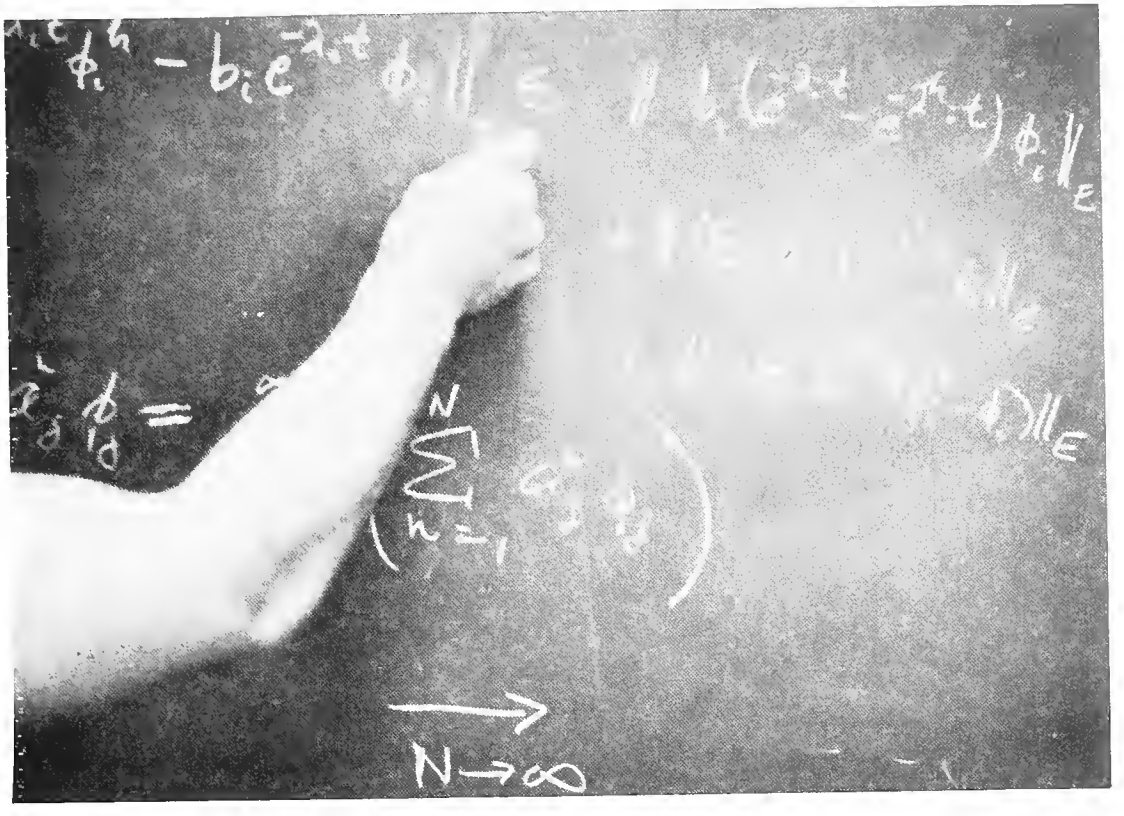
Future Plans

The coming year will again include major renovations with Buildings 12 and 12A. These renovations will in essence complete the long ranged plans developed several years ago and allow for adequate physical security for the central computer complex. As further guidance on the EEO program is received, we may have to initiate new monitoring systems to evaluate our performance in this area. There will undoubtedly be new administrative managerial requirements and modifications of old ones forthcoming from the NIH, the PHS, the Department, the GSA and the Civil Service Commision.

Project Control Officer Mary Allen and her staff run a pilot survey of the NIH users of DCRT services to determine the extent to which these services support major categories of NIH work.

LABORATORY OF APPLIED STUDIES

Eugene K. Harris
Chief



LAS began research on the development of adaptive finite element schemes which seek optimal mesh refinement strategies for the solution of reaction-diffusion systems.

I. SUMMARY OF ACTIVITIES

Functions

The Laboratory of Applied Studies (LAS) has three main purposes:

- in collaboration with biomedical scientists, to apply mathematical theory and computing science to the construction, testing and improvement of mathematical models of physiological processes, particularly reaction-diffusion processes, transport of substrate to tissues and models of receptor - ligand binding kinetics;
- in collaboration with clinicians, to develop and apply mathematical or statistical theory and computer programming to improve diagnosis of disease and assessment of treatment;
- to engage in independent research in applied mathematics, statistics and computer systems necessary to provide a sound theoretical basis for collaborative studies, and to insure that state-of-the-art mathematical and computational methods are available as research tools at the NIH.

These primary functions of the Laboratory are carried out through two sections:

1. Applied Mathematics Section (John E. Fletcher, Ph.D., Chief). The staff of 6 in this Section includes, at the doctoral level, an applied mathematician (Chief), a computer scientist, a biomathematician, and a physician-scientist, as well as an M.S.-level mathematician, and (part-time) a graduate student in mathematics with M.S. degree.

2. Medical Applications Section (James J. Bailey, M.D., Chief). The staff of 6 in this Section includes, at the doctoral level, two physician-scientists and an electronics engineer as well as two computer systems analysts and a (part-time) graduate student (M.S. degree) in electronic engineering.

The Chief, LAS, is a biostatistician. The specific research areas of these scientists are described in the individual project reports.

Scope of Work

The Laboratory of Applied Studies works on projects in basic and clinical biomedical science. In large part these go on in collaboration with other groups at NIH and elsewhere in the U.S. and abroad. The collaborating investigators this year included:

- biochemists and pharmacologists - at U. of Iowa, Medical College of Virginia, and other universities in the U.S. and in France, working on models for receptors of drugs or other ligands, and the kinetics of enzymes in membranes;
- physiologists and chemical engineers - in the U.S., U.K., Scandinavia, and Germany studying the transport of substrate within the microcirculation;
- clinicians - at NIH in the cardiology, pulmonary branches of NHLBI, the arthritis and rheumatism branch of NIAMDD, the medical intensive care unit, CC, and the departments of diagnostic radiology and diagnostic imaging, CC;
- clinical chemists and pathologists - at NIH (Clin. Path. Dept., CC), elsewhere in the U.S., in the U.K. and in Japan, engaged in the collection of and study of reference values in laboratory medicine;
- electrocardiologists and biomedical engineers, in the U.S., Canada and Europe concerned with improved algorithms for computer-based interpretation of ECG's.

During FY 79 LAS staff members participated in various teaching and consulting (or advisory) activities:

J. Fletcher continues to serve as Chairman of the Mathematics Department, FAES, and taught ordinary differential equations in the NIH graduate school;

J. Bailey continues as a member of a site-visiting team for NHLBI concerned with computer analysis of exercise ECG's. He also serves as consultant on common standards for quantitative electrocardiography for a public health program sponsored by the European Economic Community;

E. Harris continues to be a consultant in applied statistics to the Food and Drug Administration's Division of Medical Devices and Diagnostic Products. Dr. Harris also serves as consultant statistician to the Expert Panel on the Theory of Reference Values of the International Federation of Clinical Chemistry;

E. Hill is an adjunct associate professor of computer science at Howard University.

Highlights of Year's Activities

The three projects described in this section provide a brief view of selected accomplishments in each of the two sections and the Office of the Chief. A more complete description of all LAS projects appears in the Individual Research Projects Report.

- Efficient, flexible numerical methods for solving nonlinear partial differential equations implemented on NIH 370 computer system: The mathematical models developed by J. Fletcher and B. Bunow of the Applied Mathematics Section to describe time-dependent reaction-diffusion and transport processes in biological systems consist of nonlinear ordinary and partial differential equations. Numerical methods required to solve these either do not exist at present or demand very large and costly amounts of computer time. During FY 79, Drs. Fletcher and Bunow with the aid of M. Bieterman of the AMS, have tested and installed on the NIH 370 computer system several highly efficient finite element programs for solving such equations in two dimensions. Research was begun on the development of adaptive finite element schemes which allow optimal strategies of choosing time and space meshes for the numerical solution of time-dependent reaction-diffusion systems.

  In addition, finite difference methods are being explored to solve models of capillary transport processes. If successful, these procedures will greatly reduce the costs of applying the complex mathematical models needed to describe time dependent processes found in living systems.
- Detection of segmental renal artery disease using scintigraphic functional maps: Previous work by T. Stibolt and M. Douglas (Applied Mathematics Section and Medical Systems Section, LAS) and E. Jones (Diagnostic Imaging Branch, CC) has shown a significant advance in radionuclide renography through the use of computer-generated functional maps, which are now in routine clinical use at several research institutions in the United States and Europe. During FY 79 new algorithms for edge-detection and masking were designed and incorporated into the functional mapping programs. A change in radionuclide (from I-131 to I-123) has resulted in a 15 or 20 to 1 improvement in signal-to-noise ratio. With the new algorithms and the new radionuclide five dogs were studied following surgical ligation of a segmental renal artery. In some of the dogs the dynamic effect of the lesion was revealed in the functional maps, whereas contrast angiography failed to reveal the lesion in any of the dogs. The functional maps will be used in FY 79-80 to study large populations of patients with renal artery disease and hypertension before and after therapy to improve regional renal blood flow. This tool will be a sensitive means of following the effects of such therapy.

- Statistical criteria developed for judging the probable importance of an observed change between serial blood chemistry tests: E. Harris (LAS), G. Shakarji (DMB), S. Brown (Clinical Research Centre, Medical Research Council, U.K.): Physicians vary considerably in the criteria they use to assess the significance of an observed difference between measurements of a biochemical constituent in the same individual on two successive occasions. These variations depend in large part on presumed laboratory imprecision and on the physician's experience with that type of patient. However, numerous recent studies both at NIH and elsewhere have demonstrated that healthy persons vary substantially in both mean and standard deviation of results over fixed time periods (e.g., week-to-week, or year-to-year). Thus, a given difference between two successive lab tests may be medically significant in an individual who generally maintains close physiological control, but merely random variability in another person whose physiology does not closely regulate the constituent measured. Using recent data on the distribution of within-person standard deviations, methods have been developed for estimating the proportion of healthy persons in whom a specified change is likely (stated probability) to be at least statistically significant. Thus, for the first time, an objective, quantitative basis (involving biological as well as analytic variation) has been reached for assessing various proposed thresholds of acceptable changes over time in the blood chemistries of healthy persons.

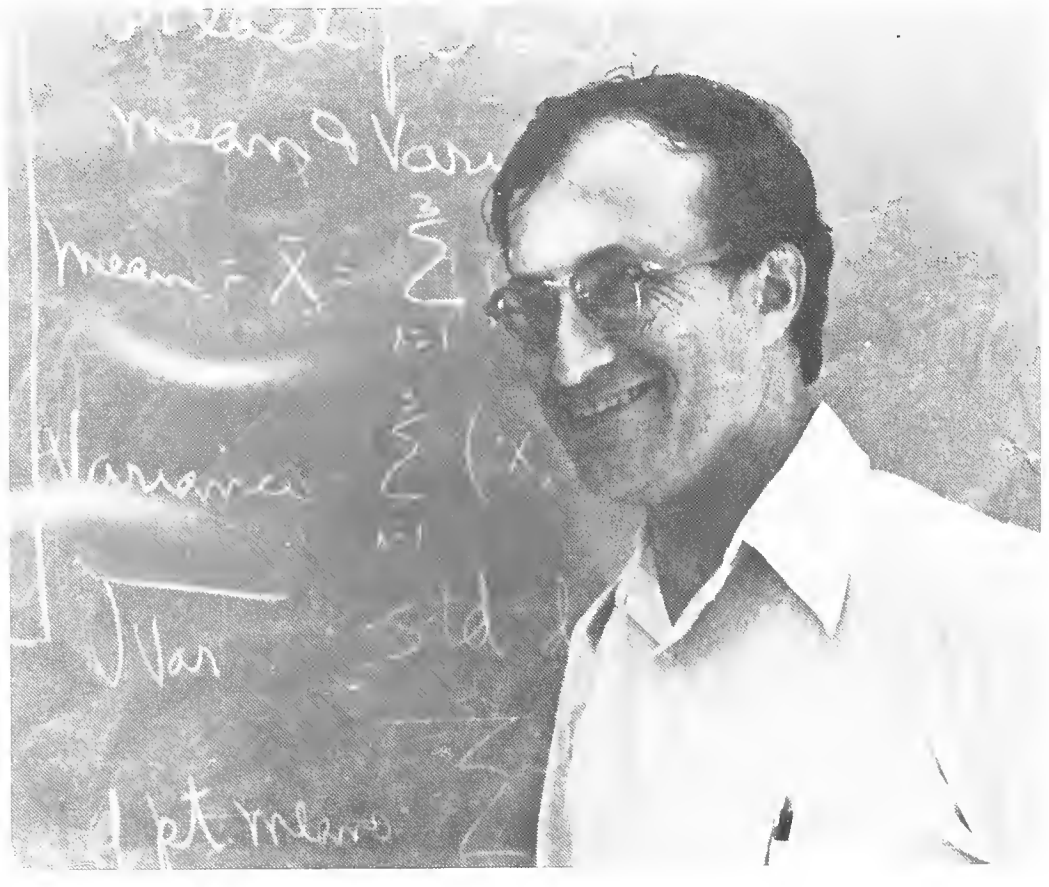
Staff Changes in FY 79

- LAS is pleased to welcome Richard Shrager, mathematician, to the Laboratory's Applied Mathematics Section. In addition to his independent research, Mr. Shrager is an active consultant to and collaborator with many NIH scientists.

- We are sorry to lose Dr. Edward Hill, computer scientist, who has transferred to the Department of Energy after 10 years with LAS, and Dr. Bruce Line, senior medical staff fellow who has rejoined the Diagnostic Imaging Branch, CC after 3 years with LAS.

Future Plans

As noted above, LAS scientists in FY 80 will continue their studies of efficient numerical methods for solving complex mathematical models. Further, several LAS projects will be heavily involved in applications to patient care or in the use of patient data. These include the study of functional mapping in renal hypertension; collection of data on pulmonary function and scintigraphic tests from normal volunteers; testing models of pulmonary gas exchange and computer simulations of electrolyte balance with data from patients in intensive care units; multivariate time series analysis of biochemical measurements in large groups of healthy subjects. Finally, we anticipate progress in the development of mathematical and physical models to support our newly-begun collaborative effort in electron-loss spectroscopy.



During FY79, LAS staff members participated in various teaching and consulting activities. LAS Chief Dr. Eugene Harris continues to be a consultant in applied statistics to the Food and Drug Administration's Division of Medical Devices and Diagnostic Products.

II. ANNOTATED PROJECT AND ACTIVITIES LIST

- Clinical research, patient care, epidemiology

  Simulation of physiological systems: E. Hill, J. Fletcher, E. Harris (LAS); B. McLees (CC): Exploration and testing of computer programs simulating responses of physiological systems to determine the usefulness of such programs as consultants or quality control mechanisms in patient care.

  Computer aided analysis of electrocardiograms: J. Bailey, M. Horton (LAS): Separate studies, conducted in collaboration with cardiologists and biomedical engineers in U.S. and abroad to evaluate the utility of leading computer programs for ECG interpretation, and to search for optimal computer-based methods of extracting medically significant ECG patterns.

  Computer systems for diagnostic imaging: J. Bailey, M. Douglas, B. Line (LAS); H. Ostrow (CSL); M. Green and others (Diagnostic Imaging, CC): Development and application of computer systems to such diagnostic imaging activities as ECG-gated radionuclide angiocardiography, functional mapping and other scintigraphic studies of kidney, brain, heart and lung.

  Computer-based studies in ultrasonography: T. Stibolt, Jr., M. Douglas, J. Bailey (LAS); B. Maron, J. Gottdiener (NHLBI); S. Leighton (BEIB, DRS): Development of computer systems for image enhancement and 3-dimensional reconstruction from ultrasound data, particularly data derived from scanning of the heart and intra-abdominal organs.

  Statistical research in clinical pathology: E. Harris (LAS); G. Shakarji (DMB); clinical chemists in California, U.K., Japan and elsewhere: Application of variance component and time series analysis to description of reference distributions of clinical laboratory tests, to serial studies of normal biochemistries, and to the design of criteria for recommended precision and accuracy of analytic methods.

- Laboratory investigation

  Mathematical modeling of biological processes: J. Fletcher (LAS); A. Spector (University of Iowa): Development and application of mathematical models in studies of substrate transport in the microcirculation, diffusion processes in physiology, and macromolecule-ligand binding equilibria.

Mechanisms of active transport; biochemical kinetics: B. Bunow (LAS); J. Rinzel (NIAMDD); J. De Simone et al. (Medical College of Virginia): Experimental and mathematical studies of the energy mechanisms for active transport, and of multi-state biochemical kinetics in cells and membranes.

Computer-based modeling of pulmonary gas exhange: Many LAS staff members; staff of Diagnostic Imaging (CC), and Pulmonary Laboratory (NHLBI). Utilizing scintigraphic and other clinical data on lung function to construct sound mathematical and computer-based models of ventilation and perfusion in the lung.

Hybrid computing to analyze physiologic signals and construct simulation models: E. Pottala, A. Mitz (LAS); various I/D scientists: Using LAS minicomputer system (MAC-16) for hardware simulation of physiologic functions (e.g., retinal cell activity) and analysis of analog signals (myogram, ultrasonogram, etc.).

Image processing in electron-loss spectroscopy: E. Pottala, M. Douglas (LAS); K. Gorlen (CSL, DCRT); J. Costa (NIMH); C. Fiori (BEIB, DDR) and others: Development and implementation of mathematical models and image enhancement techniques to analyze computer-acquired information from electron-loss and X-ray spectra indicating the location of extremely small quantities of important chemical elements and active protein molecules within cells.

- Computer research and technique development

General mathematical and computational methods: E. Hill (LAS); R. Shrager (LAS, formerly of LSMM): Study of methods of fitting non-linear models utilizing other than least squares criteria. Evaluating methods of organizing large data files for rapid storage and retrieval.

Numerical methods for the solution of mathematical models describing reaction-diffusion and other processes in biological systems: M. Bieterman, J. Fletcher, B. Bunow (LAS); I. Babuska (U. of Maryland): Study, development and implementation of efficient, flexible numerical methods for the solution of nonlinear ordinary and partial differential equations involved in modeling important physiological processes.

III. PUBLICATIONS AND PRESENTATIONS LIST

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SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00035-03 LAS

PERIOD COVERED
October 1,1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Mathematical Models and Simulation Programs in Physiology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. Hill	Computer Systems Analyst	LAS DCRT
OTHER:	J. Fletcher	Mathematician, Chief	LAS DCRT
	E. Harris	Statistician, Chief	LAS DCRT
	B. MacLees	Chief	MICU CC

COOPERATING UNITS (if any)
none

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.4	.4	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves the identification and classification of various simulation programs used in physiology. These programs are being examined for utility in a clinical environment, accuracy of representation of normal and abnormal physiologic conditions, and the identification of areas of defective or missing physiologic relationships. The programs are being tested and evaluated. The outcome of the evaluation will be used to develop a more representive model to reflect the current state of knowledge in physiology.

Background and Objectives:

The objective of this project is to investigate the use of simulation programs in physiology as diagnostic and patient management aids to physicians and other clinical staff. Several biomedical researchers are using the programs to check their usefulness in physiology as diagnostic and patient management aids to physicians and clinical staff.

Significance to Biomedical Research:

Simulations offer the clinician the oppportunity to try a proposed or alternative course of medical treatment on an ideal (computer) patient, without the attendant risk of injury to the actual patient.

Progress in FY 79:

The computer simulation of electrolyte and acid-base disorders is the first simulation program to be tried in a clinical setting at the NIH. This model was chosen because elecrolyte and acid-base equilibrium data can be measured. The simulation program has been described and demonstrated during the NIH Computers in Clinical Medicine Seminar. It was found to be useful as a teaching aid. A copy of this program has been implemented for B. MacLees (MICU, CC) and other researchers for use in a clinical environment, and as a training aid. At the present time, the project is collecting comments from the user-researchers about the usefulness of the program.

Proposed Course:

Feasibility studies are being conducted to determine the utility of this program using real patient input from clinical settings and using the results as a guide to patient management. Pending the outcome of these studies, new simulators will be developed to approximate the interdependent pathways in physiological structures. This stage of development will require a continuing effort, requiring the cooperation of the interested clinical laboratories. The refinement of the program will involve the testing of the acid-base balance program with existing data on electrolyte, blood gas, and pH measurements from patients before and after specific therapeutic intervention. Feedback from the researchers will be used to develop a more meanful model to approximate physiologic structures.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00005-09 LAS

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Mathematical Models of Binding Equilibria

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.E. Fletcher	Chief, Applied Mathematics Section	LAS	DCRT
OTHERS:	E. Hill	Computer Scientist, AMS	LAS	DCRT
	R. Shrager	Mathematician, AMS (formerly of LSM, DCRT)	LAS	DCRT
	A. Spector	Professor, Univ. of Iowa Medical School		
	L. Hoffman	Professor, Dept. of Microbiology Univ. of Iowa Medical School		

COOPERATING UNITS (if any)
none

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.5	.5	

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is concerned with mathematical models of ligand-receptor or ligand-macromolecule binding studies at equilibrium. Models are analyzed for mathematical as well as for biological validity and are studied to determine their suitability for fitting to experimentally determined laboratory data. The appropriateness of various fitting criteria are studied, and general guidelines and computational algorithms are designed for interactive model fitting.

Background:

Mathematical models of macromolecule-ligand binding equilibria, have been investigated since 1966. This continuing effort has revised many of the concepts related to the binding of ligands to macromolecules, particularly small ions to proteins. It has produced an interactive methodology for the fitting of models to data and has developed other computer oriented tools for the analysis of data from laboratory experiments.

Significance to Biomedical Research:

The fitting of models to experimentally obtained data is a procedure used to estimate unknown parameters in mathematical models. The proper choice of a model, a choice of goodness of fit criteria, and the ability to estimate the unknown parameters is a basic need of biomedical research. Such procedures broaden biomedical knowledge and add to basic scientific knowledge only if the fitted models represent the underlying biological process, and the unknown parameters can be readily and accurately estimated. A thorough and continuing critique of such models and their validity for the interpretation of current laboratory and clinical experiments is therefore essential to the progress of science.

Progress in FY 79:

The previous ten years of research in this area is being collected in the form of a technical report. This report details the various alternative models, graphical presentations of data, and algorithms for fitting models to data. New fitting algorithms are now available for fitting with other than the least squares criteria. Publication is expected in FY 80.

Proposed Course:

Applications of existing and new methodology to data analysis will continue to be made as they are requested by collaborating laboratories. Some new concepts in membrane-receptor studies are being considered and experimental studies such as the analysis of cholesterol exchange in lipid bilayers are under study. The dominant direction of this project will continue to be in the examination of the binding and exchange of lipids, fatty acids, and cholesterol in laboratory experiments. The level of effort will depend on the success of new experimental designs.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00002-09 LAS

PERIOD COVERED
October 1, 1977 to September 30, 1978.

TITLE OF PROJECT (80 characters or less)

Computer Aided Analysis of Electrocardiograms

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Bailey	Chief, MAS	LAS	DCRT
	M.R. Horton	Computer Systems Analyst	LAS	DCRT
	J. Gottdiener	Chief, ECG Laboratory	CB	NHLBI
OTHERS:	S. Allen	Medical Research Analyst	CSL	DCRT
	M.E. Womble, Aeromedical Cybernetics Branch, Brooks AFB, Texas			
	P. MacFarlane, Medical Cardiology, Glasgow Royal Infirmary, Scotland			

COOPERATING UNITS (if any)

none

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	1.2	0.1

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

These studies continuing since 1970 have been directed toward the evaluation of accuracy, clinical utility, and cost effectiveness of various computer systems for analysis of routine electrocardiograms (ECG's). Further studies will involve new methods of feature extraction and design of criteria by computer techniques.

Background and Objectives:

In the past fifteen years numerous computer programs implemented upon a variety of computer systems have been developed for analysis of routine ECG's. Computer processing of ECG's has become a sizeable enterprise in many parts of the country, including both commercial bureaus offering service for a fee and non-commercial (academic or government) centers establishing the capability for themselves.

Since 1970, LAS in collaboration with the Cardiology Branch (CB), NHLBI has studied several programs to determine which, if any, would be useful to implement on the NIH campus. As a result of this work, an evaluation methodology was evolved which was published in 1974 and has become one of the standard references in the field. Although a program was selected and implemented in 1974 for daily use at NIH, additional programs and other computer systems continue to be evaluated as possible improvements to the NIH system with regard to cost and accuracy. Past evaluations have included the ECAN-D program (1964), the Mayo-IBM program (1968), the experimental IBM program (1971), and the AVA 3.4 (Pipberger) program (1975). Guidelines for evaluation of ECG programs which were developed by LAS have been adopted by the American College of Cardiology.

Progress during FY 79:

A series of 300 ECG's were collected on patients in the Glasgow Royal Infirmary, (GRI), Scotland. Clinical documentation of the patient's cardiovascular status by non ECG means in the form of enzyme studies, cardiac catheter laboratory data, etc. was obtained whenever such investigations were warranted, i.e. in most cases. The standard 12 lead ECG data was analyzed by the IBM program at NIH; modified McFee lead (XYZ) ECG data was analyzed by a program developed at GRI. The results of these two programs were compared with respect to accuracy where clinical documentation exists and with respect to cardiologist agreement in all other cases. A manuscript has been submitted to Circulation.

A method, published in 1974, for using interleaved digital samplings from the same analog tracing to test reproducibility of programs has been extended and applied to the ECAN-E program (1975) and Version 2 of the IBM program (1976) (refs 1-3).

Members of LAS and CSL developed specifications for a minicomputer system to be dedicated to ECG analysis which the Clinical Center plans to procure. A Request-for-Proposals has been sent out.

Significance:

The estimated number of computer-processed ECG's in North America in 1971 was 600,000 and in 1978 it was 6.3 million. In

view of this increase in computer usage, it will become even more important to have methodologies and guidelines by which ECG computer systems can be evaluated.

These studies seek to establish the diagnostic limits of ECG itself and the degree to which computerized algorithms may achieve these limits. Important evaluation methodology continues to be developed, which may have a significant impact on the further diffusion of computer technology in electrocardiography.

Proposed Course:

The testing of ECG programs developed by other organizations has largely been completed in FY 79; however, some additional evaluations will need to be made in selecting a minicomputer system for the Clinical Center.

Most ECG programs today use a feature extraction scheme which supposedly imitates the human reader; however, these may not be the optimal features for computer programs. Therefore, further work in this area will involve collaboration with the Aeromedical Branch at Brooks Air Force Base in investigation of various feature extraction schemes, including the use of Karhunen-Loeve (KL) expansions.

KL functions are orthogonal functions with shapes similar to various ECG patterns and are derived from a large collection of ECG's. KL expansions have been shown to be useful for noise filtering and data compression as well as having potential for a computer-based scheme for diagnostic classification.

Publications and Abstracts:

Bailey, J.J., Horton, M.R.: Reproducibility of version 2 of the IBM program with and without the serial comparison option. The Fifth International Congress of Electrocardiology, 1978 (in press).

Bailey, J.J., Horton, M.R., Goldman, A.P.: Testing of updated programs for ECG analysis. Proceedings of the Second Annual Symposium on Computer Application in Medical Care. IEEE Catalog 78CH1413-4, 1978, pp. 606-609.

Bailey, J.J., Horton, M.R., Goldman, A.P.: Performance of updated programs for ECG analysis: comparison of ECAN-E with ECAN-D. Proceedings of the Eighth Annual Conference of the Society for Computer Medicine, Minneapolis, Minnesota, 1978, pp. 2.3.9-11.

Bailey, J.J., Horton, M.R.: Type A electrocardiogram data bases: purpose and development. Proceedings of International Federation in Information Processing TC4 "Optimization of Computer-ECG Processing", 1979 (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00003-08 LAS

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Computer Systems for Nuclear Medicine

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Bailey	Chief Med. Appl. Sec	LAS	DCRT
	M.V. Green	Ch, Appl. Physics Sec	NM	CC
	M.A. Douglas	Comp. Syst Analyst	LAS	DCRT
	T.B. Stibolt, Jr.	Senior Staff Fellow	LAS	DCRT
OTHERS:	B.R. Line	Medical Research Analyst	LAS	DCRT
	H.G. Ostrow	Engineer	CSL	DCRT
	S.L. Bacharach	Physicist	NM	CC
	A.E. Jones	Chief, Diagnostic Imaging	NM	CC
	G.S. Johnston	Chief	NM	CC

COOPERATING UNITS (if any)
Nuclear Medicine Department, CC, NIH
Computer Systems Laboratory, DCRT, NIH

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.1	3.0	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves computer-based mathematical analysis, pattern recognition, and image processing in support of diagnostic activities in the Nuclear Medicine Department of the Clinical Center and collaborating Institutes. Applications include computerized ECG-gated radionuclide angiocardiography and myocardial perfusion scintigraphy, renal dynamics, and pulmonary ventilation-perfusion relationships.

Background and Objectives:

Since FY 72 LAS and CSL in collaboration with the Nuclear Medicine Department, CC have been involved in the acquisition and development of several minicomputer systems which gather and process data from the scintillation cameras in the Nuclear Medicine Department.

The objective of this program is continuing development of computer based algorithms, which have already found wide-ranging applications, including: fitting mathematical models; mapping the parameters of such models over time and in different regions of an organ; image processing; interpolation, expansion, and contraction of image arrays; and pattern recognition.

Progress during FY 79:

The minicomputer systemsin the Nuclear Medicine Department have been upgraded to new, faster CPU's and from magnetic tape to disk drives. These hardware upgrades, together with software refinements have resulted in greater ease of use, especially by the Nuclear Medicine technicians, and improved turnaround, making the results more readily available to clinicians.

There has been continued development of IMAGE, a DEC-10 based package of image processing routines begun in FY 76; it has been enlarged to allow a wider range of options for edge-detector methods, smoothing methods, display techniques and new methods for background minimization.

An outgrowth of IMAGE is PSTACK, also a DEC-10 based system which allows the application of various image processing algorithms to a stack of pictures with a single command. It has been designed to handle dynamic scintigraphic images so that spatial data can be augmented with temporal data - i.e. processing of a moving picture. It also allows dual processing of two picture stacks so that the results of two different algorithms can be compared side-by-side, visually and quantitatively. Various processing options include: background subtraction by value, by percent of maximum, or by variable mesh; automatic masking and time function generation; image rotation and clipping; linear/nonlinear modification of gray scale; temporal and/or spatial smoothing by weighted average, by statistical bounding, by median replacement or by iterative replacement; and "sharpening" by a selection of convolution operators.

LAS has acquired a DeAnza VC 2000 image display terminal allowing interactive design of image processing applications and generation of movies.

While the main thrust of IMAGE, PSTACK, and the DeAnza terminal has been towards processing dynamic scintigraphic images, it is anticipated that these methods will also find ready application in ultrasound and electron-microscopy images (see reports on diagnostic ultrasound and electron-microscopy).

Automatic edge detection methods, designed and tested by means of IMAGE and PSTACK have been successfully applied to radionuclide angiograms (ref 1), renal scintigrams, and pulmonary scintigrams.

During FY 79 for the first time dual radionuclide studies of the heart, i.e. angiography (blood pool) and myocardial perfusion with thallium - 201, have been accomplished. This allows areas of wall motion abnormalities to be correlated with areas of decreased perfusion in a semiquantitative way.

Previous work in FY 76 showed a significant enhancement of radionuclide renography by the use of functional maps and since FY 77 functional maps have come into routine clinical use in the Diagnostic Imaging Branch. A series of 5 dogs was studied before and after surgical ligation of a segmental renal artery. Using the functional mapping techniques, it was possible in 3 dogs to demonstrate the presence of a defect. Defects were not detected in any dog with contrast angiography, the current definitive technique. This work was presented at the Society of Nuclear Medicine Meeting in June.

The location and degree of severity of inflammatory processes in the lung has been studied in several types of disease, using a method for quantifying the uptake of radio gallium in the lung (refs. 3-4).

Significance:

Scintigraphy is a noninvasive tool which shows considerable detail concerning the dynamic function of an organ on a regional basis. Computer processing not only enhances scintillation images but allows quantification of the dynamic function. Real time implementation of algorithms on the minicomputers allows the clinical investigator to perform repeated studies on patients with exercise or therapeutic manipulation, thus better elucidating the nature of the patient's pathophysiology.

Proposed Course:

Use of automatic edge detection in both end-diastolic and end-systolic angiographic images is being evaluated in collaboration with investigators at the University of Ulm, West Germany. Further studies of the combined use of myocardial (thallium) images and blood pool images to refine detection of regional wall motion and perfusion

and to determine "absolute" volumes, if possible, are planned. Methods for enhancing dynamic myocardial images will be extensively investigated, using IMAGE, PSTACK, and the DeAnza terminal.

Renal scintigraphy with functional mapping will be applied to a series of hypertensive patients suspected of having segmental renal arterial disease. These patients are to be treated with a new drug that has demonstrated the potential of producing local renal arterial dilatation. Additionally, some of these patients may undergo renal artery dilitation using a newly developed catheter technique. Functional mapping will be used in evaluation and follow-up of both patient groups.

Further work this year will occur in animal models. Particular emphasis will be given to renal transplant models and immune complex renal disease models.

In FY 80 the reproducibility of pulmonary scintigraphy and its correlation to pulmonary functions will be investigated in a series of normal patients (see section on Computer-based Studies in Pulmonary Pathophysiology and Respiratory Disease).

Publications and Abstracts:

Douglas, M.A., Green, M.V., Ostrow, H.G.: Evaluation of automatically generated left ventricular regions of interest in computerized ECG-gated radionuclide angiocardiography. Computers in Cardiology. 201-204, September 1978.

Green, M.V., Brady, W.R., Douglas, M.A., Borer, J.S., Ostrow, H.G., Line, B.R., Bacharach, S .L., Johnston, G.S.: Ejection fraction by count rate from gated images. Jour. Nucl. Med. 19(8):880-883, August 1978.

Brereton, H.D., Line, B.R., Londer, H.N., O'Donnell, J.F., Kent, C.H., Johnson, R.E.: Gallium scans for staging small cell lung cancer. JAMA, 240:666-667, 1978.

Line, B.R., Fulmer, J.D., Reynolds, H.Y., Roberts, W.C., Jones, A.E., Harris, E.K. Crystal, R.G.: Gallium-67 citrate scanning in the staging of idiopathic pulmonary fibrosis: correlationg with physiology, morphology and bronchoalveolar lavage. Amer. Rev. Resp. Dis., 118:355-365, 1978.

Green, M.V., Ostrow, H.G., Scott, R.N., Douglas, M.A., Bailey, J.J., Johnston, G.S.: A comparision of simultaneous measurements of systolic function in the baboon by the electromagnetic flowmeter and high frame rate, ECG-gated blood pool scintigraphy. Circulation (in press), 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00043-01 LAS

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Computer-based studies in ultrasonography

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.B. Stibolt, Jr.	LAS	DCRT
	B.J. Maron	CB	NHLBI
	J.S. Gottdiener	CB	NHLBI
	T.H. Shawker	DRD	CC
OTHERS:	M.A. Douglas	LAS	DCRT
	J.J. Bailey	LAS	DCRT
	S.B. Leighton	BEIB	DRR

COOPERATING UNITS (if any)

Radiology CC
CB NHLBI

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.4	1.2	0.2

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves collaboration of LAS, with the Cardiology Branch, NHLBI, the Diagnostic Radiology Department, CC, and Biomedical Engineering and Instrumentation Branch, DRR. It is directed toward computer-based processing for image enhancement, pattern recognition, and 3 dimensional reconstruction from ultrasound data. The principal sources of data are wide-angle, phased array echo-cardiography and B-mode, gray scale, abdominal ultrasonography.

Background and Objectives:

Ultrasonography allows non-invasive visualization of many organs without the hazard of ionizing radiation. Due to its safe nature and little or no patient discomfort, it is an excellent tool for screening and multiple repeat follow-up studies. Unfortunately, certain limitations relating to presence of bone which is completely opaque to sound waves and to processing practices make this technique fall short of its full potential. Using the computer, it is possible to overcome or circumvent many of these limitations.

Progress during FY 79:

The cardiology Branch has acquired a Varian Sector Scanner which uses a phased array transducer head. This can now be fixed to a patient's chest wall using an NIH designed support device. This device contains an integral indicator for transducer angle which allows acquisition of serial images over 50 degrees in 2 degree intervals. Programs to correct the images for beam angulation have been written and an abstract describing the technique has been submitted for presentation at the American Heart Association Scientific Meeting in 1979.

The Diagnostic Radiology Department, CC with advice and consultation from LAS has acquired equipment which gathers digital records of B-mode ultrasound images of intra-abdominal organs. The Evans and Sutherland display system at DCRT can be used to transform echo intensity to gray scale or color values in the image in any selected linear or non linear way. In this way texture information in areas which are not well seen in ordinary ultrasonograms, such as the pancreas, can be enhanced.

IMAGE a DEC-10 based package of picture processing routines and a recent outgrowth, PSTACK have been developed and updated to allow interactive application of picture processing algorithms from the De Anza terminal recently acquired by LAS (for further details, see Computer-based studies in Nuclear Medicine).

Significance:

Patients with hypertrophic cardiomyopathy are at increased risk of sudden death. Unfortunately, many of these persons are not diagnosed ante-mortum because they are asymptomatic. A reliable technique to screen those persons with a family history of hypertrophic cardiomyopathy would be of great use since prophylactic drug therapy is probably feasible. Unfortunately, many different patterns of hypertrophy appear to exist in the population afflicted. Techniques to assess the distribution of hypertrophy are needed in those patients with uncommon distributions, especially those missed by

traditional M-mode echocardiographic techniques. Additionally, it is likely that the prognosis may differ among the various patterns of hypertrophy. The determination of regional wall motion abnormalities and other parameters of left ventricular function in patients with coronary artery disease with this technique could be a very important adjunct or even supercede such determinations now being accomplished by radionuclide angiography.

B-mode abdominal echography is a widely employed technique in evaluation of many disease states involving the abdomen. In some instances, useful information is lost during the assignment of grey scale value from echo intensity. A tool to allow changing this assignment retrospectively in an interactive mode would allow testing of this hypothesis.

Proposed Course:

Groups of normal volunteers and patients with hypertrophic cardiomyopathy or coronary artery disease will be studied using this new method of echocardiography. In addition computer-based reconstruction of left ventricular anatomy in 3 dimensions from serial 2-dimensional, wide angle phased array sector scans will be undertaken.

It is anticipated that the De Anza terminal will allow IMAGE and PSTACK to be applied also to the B-scans of the abdomen.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00007-11 LAS

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Statistical Research in Clinical Pathology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.K. Harris	Chief, Lab. of Applied Studies	LAS	DCRT
OTHERS:	G. Shakarji	Supv. Systems Analyst	DMB	DCRT
	G.Z. Williams	Director, Institute for Health Research, San Francisco, CA		
	S.S. Brown	Clinical Chemistry Service Clinical Research Centre Harrow, England		
	E. A. Robertson	Clinical Pathology	CC	
	T. Yasaka	Perfect Liberty Medical Service Department Osaka, Japan		

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Applied Studies

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In cooperation with Dr. G. Z. Williams and staff of the Institute for Health Research (San Francisco), records of some 30 different biochemical and hematological tests performed annually over a 4-7 year period on several hundred healthy volunteers have been analyzed to test the behavior and usefulness of statistical forecasting models described in previous reports and publications. An initial draft of a manuscript describing the results of this work has been completed and is now undergoing review. An application of the theory of Empirical Bayesian estimation to improve accuracy of individual mean values in epidemiological studies has been published. A cooperative study with Dr. S.S. Brown (Clinical Research Centre, Harrow, U.K.) of the distribution of within-person variances of biochemical constituents in healthy volunteers and its application to the interpretation of differences between successive measurements has been completed and the report is now awaiting publication. A new study with cooperating scientists at the NIH and in Japan has begun on the application of multivariate time series theory to short series of biochemical tests.

Objectives:

To investigate applications of statistical theory, particularly the use of variance components, measures of within-person variation, and the theory of discrete time series, to the interpretation of clinical laboratory measurements and the evaluation of analytic methods.

Background and Progress during FY 79:

The database gathered through the health monitoring program of the Health Research Institute (HRI), San Francisco, represents one of the largest extant collections of serial biochemistries on normal volunteers. Hence it offers an unusual opportunity to study the suitability of various recently published statistical models and analytic methods aimed at detecting step changes and trends in short series of biochemical data from healthy persons. During the past year, statistical analysis has been completed on over 30 biochemical and hematological analytes in several hundred individuals who have undergone at least 4 annual examinations, with several weekly retests around each time of examination. Results show that a nonstationary, random walk model of within-person variation is particulary well-suited to the detection of trends in individual series. The practical effects of using forecasting ranges based on both stationary and nonstationary models are being explored in this database.

Utilizing a smaller database of weekly measurements on 37 healthy male volunteers over a 5-month period, collected in a cooperative study with the Clinical Research Centre, Harrow, England, the second of a new series of reports on normal variation has been accepted for publication and should appear before the end of 1979. This analysis focuses on the heterogeneity of intra-personal variation in each of 10 common analytes, and the effects of such heterogeneity on the applicability of commonly accepted criteria concerning the amount of change between successive observations which should trigger investigative medical activity.

During the summer of FY 79, with the aid of a graduate student in biostatistics (Ms. Emily Terwey of the University of Texas Health Sciences Center) work has begun on the application of multivariate random walk theory to the sequential forecasting of biochemical test results in short series from healthy subjects. Data has been provided from past records of an extensive ongoing health monitoring program in Japan through the kind cooperation of the Director of the data processing center for this program in Osaka.

Significance to Biomedical Research:

The definition and estimation of analytic and biological variance components provides an essential basis for the objective interpretation of clinical laboratory tests in patients and healthy persons alike. The development, testing and routine use of univariate stochastic models to describe and forecast sequential results of laboratory tests in individual cases has proven useful when applied to periodic monitoring of healthy individuals as part of a general program of preventive medicine. Introduction of multivariate models for this purpose should prove even more valuable since many laboratory tests are interpreted as part of a multi-test organ battery or in concert with other, physiologically related measurements (e.g., calcium. total protein, albumin). These methods of data analysis require the use of standard computer program packages as well as construction and implementation of special algorithms for computer-based laboratory reporting systems. A spin-off from these research efforts has been the development of versatile computer systems for storing, updating and retrieving serial information on multiple laboratory results for individual patients. These systems are currently being employed in the Hypertension-Endocrine Branch (HNLBI) and the Arthritis and Rheumatism Branch (NIAMDD). These developmental and associated consulting activities have expanded the services which DCRT offers the NIH clinical community.

Future Course:

A final report on application of univariate stochastic models to serial data from the monitoring program of the Institute for Health Research should be completed and submitted for publication early in FY 80. Current cooperative investigations of multivariate models will continue during FY 80 with at least a preliminary report of results expected to be ready by the spring of 1980. A study of the probabilities of false alarm associated with the sequential use of these forecasting models is also expected to begin during FY 80. The P.I. (E.H.) has accepted an invitation to prepare an extensive review of the general theory of reference values in healthy persons and this should be completed during FY 80. As more and more clinical pathologists, chemists and practicing physicians become interested in the application of time series models to monitoring individual patients, a certain amount of time must be devoted to suitable "packaging" of the relevant computer algorithms and communication of the programs and instructions on their use to interested users. Through such means, new cooperative studies may arise which cannot now be foreseen. In addition, it is anticipated that use of the storage, updating and retrieval programs in NIH clinical laboratories will expand and lead to collaborative research studies, particularly in the use of serial patient data to predict clinical outcome.

Publications and Abstracts:

Harris, E.K. and Shakarji, G.: Use of the population distribution to improve estimation of individual means in epidemiological studies. J. Chronic Diseases, 32: 233-243, 1979.

Harris, E.K.: Statistical principles underlying analytic goal-setting in clinical chemistry. Amer. J. of Clinical Pathology, August 1979.

Harris, E.K. and Brown, S.S.: Temporal changes in the concentrations of serum constitutents in healthy men: distributions of within-person variances and their relevance to the interpretation of differences between successive measurements. Annals of Clinical Biochemistry (in press).

Harris, E.K.: Review of statistical methods of analysis of series of biochemical test results. Annales de Biologie Clinique, 36: 194-197, 1978.

Harris, E.K.: Appropriate use of population and individual reference data in patient care. Proceedings of the Second Annual Symposium on Computer Application in Medical Care (IEEE Computer Society), November 5-9, 1978, pp. 408-409.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00044-01 LAS

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Mathematical Modeling of Substrate Transport in Physiological Environments

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.E. Fletcher	Chief, Applied Mathematics Section	LAS	DCRT
OTHER:	M. Bieterman	Mathematician, AMS	LAS	DCRT
	R. Shubert	Associate Professor Louisiana Tech. Univ.		

COOPERATING UNITS (if any)
none

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.5	.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Mathematical models of microcirculatory structure and function are developed from conceptual models into systems of coupled ordinary and/or partial differential equations. Methods of solution of these nonclassical formulations are developed and tested and satisfactory cost effective methods are used to explore the properties of these models. The results are interpreted in terms of microcirculatory physiology and are published in the scientific literature.

Objectives:

The objectives of this project are to develop mathematical models which can be used to simulate microcirculatory physiology and to explain, interpret and/or predict physiologic behavior and limits. Such models may lead to a better understanding of basic biological processes and suggest new experimental approaches to microcirculatory phemomena of biomedical and biochemical importance.

Background:

The mathematical modeling of substrate supply to tissue from the microcirculation has been under study since FY 69. The substrate of primary interest is oxygen. Such modeling studies are aimed at the prediction of threshold and critical limits of substrate supply necessary to sustain cell function under a variety of physiologic conditions. The responses of models to varying blood flow, blood hemoglobin characteristics, tissue metabloic rate, tissue binding proteins, and other physiologic parameters have been examined. The complex interaction of microcirculatory geometry, nonlinear oxygen hemoglobin dissociation properties, intracellular binding proteins, and substrate dependent metabolic rates requires such a detailed description to achieve physiologic validity. These models require the numerical solution of a system of coupled distributed parameter models which are of a nonlinear type.

Significance to Biomedical Research:

Such modeling is necessary to examine the state of local tissue microcirculatory dynamics since direct measurements are generally not possible and microcirculatory function must be inferred from boundary observations. Studies of this type have the potential of predicting tissue oxygenation and reoxygenation in ischemia, hypoxia, anemia, coronary obstructions, sickle cell anemia, shock and other conditions of substrate normal and abnormal physiology.

Progress in FY 79:

The contribution of binding proteins to substrate transport in tissue was initially considered in FY 78. A new model was developed which included the previously neglected effects of flow, capillary length and radius, and oxygen dissociation kinetics in capillary blood. The resulting mathematical model required nonclassical solution techniques. A parametric study of the steady state system has been completed and the results have been submitted for publication. A new methodology for the extended time dependent system of equations is currently being explored. Preliminary results with steady-state systems suggest that diffusion facilitation is

important at low blood flow rates and/or at high metabolic rate conditions. The principal investigator is currently participating in international conferences which are to examine the various aspects of microcirculatory modeling.

Proposed Course:

Mathematical techniques for the solution of time dependent model equations will be explored for accuracy and cost-effectiveness The numerical techniques currently under development will be applied to the models describing the complex interactions of facilitation, metabolism, and blood-oxygen extractions. Efforts will be made to consider rhythmic or periodic conditions which relate more closely to the cardiac and skeletal muscle functions.

Publications and Abstracts:

Fletcher, J.E. An Overview of Mathematical Modeling in the Microcirculation. Proceedings of 31st ACEMB meeting, Atlanta, GA., 21-25 October 1978, 384.

Fletcher, J.E., Facilitated Diffusion in a Krogh Cylinder Model, Proceedings of 3rd International Oxygen Transport to Tissue Conference (ISOTT), La Jolla, Calif, July 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00033-03 LAS

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Analysis of Coupled Transport and Biochemical Kinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	B.Bunow	Senior Staff Fellow Applied Mathematics Section	LAS	DCRT
OTHERS:	J. Kernevez	Prof. Univ. of Tech. Compiegne France		
	J. DeSimone	Prof. Medical College of Virginia		
	D. Mikulecky	Prof. Medical College of Virginia		
	G. Weiss	Chief	PSL	DCRT
	A. Kaplan		LCM	NCI
	M. Bunow	Guest Worker	LCP	NIAMDD
	J. Weinstein		LTB	NCI
	M. Bieterman	Mathematician, AMS	LAS	DCRT

COOPERATING UNITS (if any)
none

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH Bethesda, MD. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project investigates two fundamental problems in biology: (1) the role of dynamic patterns in embryology and evolution, and (2) kinetics of enzymes located in cell membranes. The first area involves a demonstration of the role which simultaneous reaction and diffusion might play in the formation of biological patterns such as organ shapes and surface markings. The second area involves investigation of the effect of diffusion limitation by cell membranes on the kinetics of enzymes contained in them. Digital computer simulation and numerical solution of partial differential equations are the main tools in these investigations.

(1) Dynamic Patterns

Background and Objectives:

The objectives of this investigation are twofold. The first is a study of dynamic patterns in reaction-diffusion systems obeying realistic biochemical kinetics. The objective here is to demonstrate that such systems can spontaneously develop patterns of concentration variation when unstructured solutions are slightly perturbed. These patterns may be stationary, periodic, or may propagate as waves. The second objective is to evaluate the hypothesis that such patterns may play a role in the formation of adult structures during embryonic development.

Significance to Biomedical Research:

Patterns generated by reaction-diffusion processes have been implicated in numerous areas of biology, including embryonic organogenesis, wound healing, and epilepsy. Several important questions are addressed about such patterns. 1) How do the patterns depend upon the geometry of the region where they appear? 2) How stable are the patterns to variations in the shape of the region or the physical and chemical parameters of the describing equations? 3) How do the patterns change as the region grows?

Progress in FY 79:

The kinetics of the enzyme uricase have been shown to produce patterns in a one dimensional spatial domain. Stationary, oscillatory and propagating patterns have been produced on this domain. A computer code using the finite element method has been completed which permits study of pattern formation in plane regions (two space dimensions) as well as on closed surfaces, such as the epithelium of a developing Drosophila egg or imaginal disk. Bifurcation analysis of of the describing equations permits us to predict where patterns will be found, but not, generally, what form the patterns will take. A manuscript summarizing accomplishments during FY 78 has appeared. A second manuscript presenting results for FY 79 has been completed and will be submitted by the the end of FY 79.

Future Course:

During FY 80 a computer code will be developed to model wave propagation on two-dimensional regions. This code will be used to investigate rotating waves, a phenomena which is observed in aggregation of Dictostelium discoideum as well as in the Zhabotinskii-Belusov reaction. Further work will be done on the formation of patterns on the egg blastoderm of Drosophila, using the finite element code developed in FY 79.

(2) Kinetics of Enzymes

Background and Objectives:

Many enzymes are bound to cell membranes or compartmentalized in specialized organelles. In either case, the access to the enzyme of reactants, products and cofactors is restricted by the relatively low permeability of the membrane structure. The effect of these membranes is generally ignored in studies of integrated metabolic function. It remains to be determined what effect their presence might have on studies of the mechanism of these enzymes or on the interpretation of data for the design of specific inhibitors.

Significance for Biomedical Research

The regulation of cellular electrolyte composition is attributed to the sodium/potassium exchange pump, an enzyme complex confined to cell surface membranes. The mechanism of this enzyme is an active research area. Among many unanswered questions about this enzyme are 1) What is the order of addition of sodium and potassium as the enzyme proceeds through the transport cycle? 2) Where does metabolic energy couple into the process? Can these questions be answered using only data from transport experiments?

Progress in FY 79:

The use of the shape of standard plots of enzyme kinetics (Lineweaver/Burke, Dixon, etc.) as a reliable indicator of the mechanism of enzymes in membranes has been shown to be unsatisfactory. Neither net flow nor unidirectional flow experiments can discriminate among several biochemically distinct models for the site of coupling of metabolic energy into the transport cycle. Two manuscripts have been completed. One has been submitted, and the second will be submitted shortly. An abstract describing current work has been accepted.

Future Course:

During FY 80 a dynamical network analyzer, SPICE, will be used to simulate temperature-jump experiments on active transport models. Methods developed in FY 79 for active transport systems will be applied to the modelling of receptor-cyclase interactions, in collaboration with D. Rodbard (RR CHI).

Publications and Abstracts:

Kernevez, J.P, Joly, G., Duban, M.C., Bunow, B., and Thomas, D.: Hysteresis, Oscillations, and Pattern Formation in Realistic Immobilized Enzyme Systems. J. Math. Biol. 7,41, 1978.

Bunow, B. Chemical Reactions and Membranes I: Linear Analysis, J. Theor. Biol. 75,51,1978.

Bunow, B. Chemical Reactions and Membranes II: Nonlinear Analysis J. Theor. Biol. 75,79, 1978.

Mikulecky, D.C., and Bunow, B. Distinction among Active Transport Models using Dynamic Simulation, Abstracts of the American Physiological Society, Fall 1979.

Kaplan, A., Weiss, E., and Bunow B. Methods for Kinetic Studies with Application to Lactate Dehydrogenase from Control and Transformed Hepatocytes. Abstracts of XI International Congress of Biochemistry 1979. (in press)

Bunow, B. and Weiss, G.H. How Chaotic is Chaos? 1979. Mathematical Biosciences (in press).

Bunow, M.R. and Bunow, B. Phase Behavior of Ganglioside-Lecithin Mixtures 1979. Biophysical Journal (in press).

Kernevez, J.P., Blanchard, G., Thomas, D. and Bunow, B. Pattern Formation and Wave Propagation in the S-A System, 1978 Springer Lecture Notes in Mathematics, (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00034-03 LAS

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Computer-based Studies in Pulmonary Pathophysiology and Respiratory Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Bailey	Chief, MAS	LAS	DCRT
	B.J. Bunow	Senior Staff Fellow	LAS	DCRT
	B.R. Line	Medical Research Analyst	LAS	DCRT
	T.B. Stibolt	Senior Staff Fellow	LAS	DCRT
	R.G. Crystal	Chief	PB	NHLBI
	A.W. Nienhuis	Chief	CHB	NHLBI
OTHERS:	J.E. Fletcher	Chief, AMS	LAS	DCRT
	E.K. Harris	Chief	LAS	DCRT
	M.R. Horton	Computer Systems Analyst	LAS	DCRT
	B.A. Keogh	Visiting Scientist	PB	NHLBI
	A.E. Jones	Chief, Diagnostic Imaging	NM	CC
	B.D. McLees	Chief, Critical Care Unit		CC
	A.R. Mitz	Engineer	LAS	DCRT

COOPERATING UNITS (if any)
Nuclear Medicine Dept., CC, Pulmonary Branch, NHLBI, Clinical Hematology Branch, NHLBI, Critical Care Unit, CC

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section, Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves a collaborative effort of LAS with the Nuclear Medicine Department, CC, the Pulmonary Branch, NHLBI, and the Medical Intensive Care Unit, CC. It is directed toward a deeper understanding of pulmonary pathophysiology through the constuction of computer-based models of pulmonary gas exchange and respiratory mechanics and comparisons of model predictions with real patient data.

Background and Objectives:

Numerous attempts have been made in the past to quantify pulmonary function. Inhomogeneities in the lung required certain simplifying assumptions to be made which tended to obscure the true nature of lung function. Furthermore, certain nonlinearities inherent in the lung system allowed only partial quantitative models and sometimes these could only be expressed in the form of nomograms of graphs.

Within recent years it has been possible to apply computer technology to numerous diagnostic tools, viz. spirometry, dynamic compliance studies, multiple inert gas studies, pulmonary scintigraphy, cardiac catheter studies, and blood gas studies.

This program involves the Pulmonary Branch, and the Clinical Hematology Branch, NHLBI; the Medical Intensive Care unit, CC; the Nuclear Medicine Department, CC; and the Laboratory of Applied Studies, DCRT. The objectives include the use of computer technology to refine diagnostic methods and to construct models for pulmonary gas exchange and respiratory mechanics. For example in FY 78 a computer simulation model was developed to test the accuracy and precision of various methods for extracting ventilation parameters from radioxenon studies of the lung. The simulation model showed how the results are affected by variations due to counting statistics and revealed how much improvement could be obtained through the use of a better isotope (xenon 127 instead of xenon 133), by increased dosage over a shorter time, and by using more pixels to represent a lung compartment (ref 1).

Also in FY 78 the Kelman procedure which relates gas tensions and contents in blood for given values of hemoglobin, hematocrit, pH, etc. was revised to incorporate Adair binding constants for hemoglobin, to remove unnecessary terms in the formulae and also sources of numerical imprecision, and to utilize more efficient computer algorithms.

Progress in FY 79:

A method using radiogallium citrate to tag white cells was used to study active inflammatory processes in the lung and to correlate regions of inflammation with regions of ventilation-perfusion abnormalities (refs. 2-4).

The NIH implementation of the isopleth (Kelman) model for blood gases allows global V/Q ratios and respiratory quotients to be estimated when both mixed venous and systemic arterial gas tensions are known. The data collected on the few patients so

far has shown some unexpected discrepancies between model predictions and laboratory values. Whether this is caused by failings in the model or problems with obtaining reliable values for gas tension requires further study.

Also in FY 79 analog devices(physiological signal amplifiers) have been set up in the Pulmonary Function Laboratory so that pressure volume loops and dynamic compliance data can be recorded. At present the data is digitized by the LAS minicomputer and the plots and calculations are done with the DEC-10 system. It is anticipated that automatic processing of this data will be more reliable and far less tedious than the traditional manual methods of analysis. Furthermore, this system will allow investigators to study the relationship of dynamic compliance and other parameters of respiratory function, gas exchange, etc. in a large population of patients with varying degrees of disease.

In meetings with LAS, the Pulmonary Branch, and the Clinical Hematology Branch the diagnostic and prognostic use of exercise studies and the comparison with resting studies has been extensively discussed.

Significance:

These computer-based models when combined with data from scintillation, cardiac catheter, and pulmonary laboratory studies should allow a quantitative description of pulmonary pathophysiology on a regional basis. They should allow separation of diseases (e.g. bronchitis from emphysema), separation of disease components (destructive vs. restrictive vs. vascular), assessment of severity of disease component, and prediction of the degree to which each component compromises overall pulmonary function.

In certain diseases of lungs, blood (e.g. hemoglobinopathy), and cardiovascular system, the assessment of the patient's condition at various points in the course of disease may be no better than a subjective impression given by the patient, his family, or his physician. An alternative method of assessment which could be more objective involves the use of continuous exercise; one can evaluate the overall ability of the patient to meet the demands of exercise by monitoring his ECG, blood pressure, blood gases and lactate, oxygen comsumption, etc., in a reliable and reproducible manner. The detection of "anaerobic threshold" may be of particular clinical importance when considering response to therapy or disease progression.

Proposed Course:

In FY 79 a protocol for study of normal volunteers was designed and approved. The reproducibility of ventilation-

perfusion scintigraphy, the sensitivity and spatial resolution of regional scintigraphy, and relationship of scintigraphic parameters to other measures of pulmonary function are to be systematically studied in this population. The discrepancies between the isopleth model and measured blood gases are also to be further investigated in additional cases. The potential use of resting thallium scintigrams to detect right ventricular overload in patients with pulmonary and other various cases will also be studied.

The Clinical Hematology Branch has been operating an exercise lab; in collaboration with LAS and the Pulmonary Branch they propose to implement computer processing of this data, a major aim of which will be to define and detect anaerobic threshold in a variety of patients as mentioned above.

Publications and Abstracts:

Bunow, B., Line, B.R., Horton, M.R., Weiss, G.H.: Regional ventilatory clearance by xenon scintigraphy: A critical evaluation of two-estimation procedures. J. Nucl. Med. 20 703-710, 1979.

Line, B.R., Fulmer., J.D., Reynolds, H.Y., Roberts, W.C., Jones, A.E., Harris, E.K., and Crystal, R.G.: Gallium-67 citrate scanning in the staging of idiopathic pulmonary fibrosis: Correlation with physiology, morphology and bronchoalveolar lavage. Amer. Rev. Resp. Dis., 1978, 118 355-365.

Brereton, H.D., Line, B.R., Londer, H.N., O'Donnel, J.F., Kent, C.H., and Johnson, R.E.: Gallium scans for staging small cell lung cancer. JAMA, 1978 240 666-667.

Crystal, R.G., Fulmer, J.D., Baum, B.J., Bernardo, J. Bradley, K.H., Bruel, S.D., Elson, N.A., Fells, G.A., Ferrans, V.J., Gadek, J.E., Hunninghake, G.W., Kawanami, O., Kelman, J.A., Line, B.R., McDonald, J.A., McLees, B.D., Roberts, W.C., Rosenberg, D.M., Tolstoshev, P., Von Gal, E., Weinberger, S.E.: Cells, collagen and idiopathic pulmonary fibrosis. Lung 155, 199-224, 1978.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00004-08 LAS

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Investigation of Hybrid Computing for the Construction of Simulation Models and for the Analysis of Physiologic Signals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.W. Pottala	Elec. Engineer	LAS	DCRT
OTHERS:	J.J. Bailey	Chief, MAS	LAS	DCRT
	A.R. Mitz	Elec. Engineer	LAS	DCRT
	I. Yaar	Visiting Scientist	MNB	NINCDS
	W.C. Van Arsdale	Pharmacologist	DDB	FDA

COOPERATING UNITS (if any)
Medical Neurology Branch, NINCDS
Division Cardio-Renal Drug Products, FDA

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	.1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project was undertaken to develop physiologic simulation models using hybrid computing and also to use hybrid computing techniques to analyze physiologic signals such as electrocardiogram, electroencephalogram, ultrasonogram, and electromyogram.

Background and Objectives:

In some simulation models, certain pieces or functions can be split off and implemented in hardware circuitry or a set of microprocessors. This has several advantages. First, parallel processing is allowed, which can shorten computing time and make interactive model testing feasible. Second, the hardware circuitry or microprocessors are usually quite inexpensive. And third, some models are so complicated and extensive, that their implementation on a large scale digital computer is not feasible; whereas with hybrid computing, such models may be achieved. An example was the model of the Purkinje network in the alligator cerebellum which required a system of 35 cells connected by nonlinear differential equations (completed in FY 76).

Since FY 72 the LAS Laboratory minicomputer system (MAC 16) has been developed and utilized for various projects including (1) the construction of physiologic simulation models and (2) the processing of physiologic signals. Since FY 72 the system has been interfaced with the Marquette tape drive (for routine ECG's from the Clinical Center); with the Honeywell 7600 analog tape transport; with a general purpose switch-filter network; with a real time spectral analyzer and ensemble averager; and with a neural control panel for simulation of neural networks (FY 75) and central nervous system subsystems (cerebellum, FY 76).

A general advantage of this system is that an investigator can automatically pre-process (edit, filter, and digitize) dynamic physiologic data so that optimal use of a large scale digital computer can be obtained. This was demonstrated in electromyograms from subjects on a muscle fatigue protocol studied by the National Institute of Occupational Safety and Health (FY 75). This facility was also used for electrocardiogram (ECG) and ventricular pressure data in monkeys (FY 76) and also ECG data from Glasgow Royal Infirmary (see ECG section).

Progress During FY 79:

The Laboratory of Neurophysiology, NINCDS, is studying the electrophysiology of the retina of the larvae tiger salmander. The Baylor-Hodgkin-Lamb model of a cone cell requires six compartments connected by six linear differential equations and three compartments involving sodium and potassium fluxes related by three nonlinear differential equations. This model has been implemented in hardware by LAS (ref. 1-2). It was also implemented in software on the PDP-10 so that the hardware model could be thoroughly checked out. The model parameters were adjusted to best fit the actual photoresponses (membrane potential) recorded intracellularly from cones in the retina of the larva tiger salamander. Stimuli consisted of flashes and steps of light. The responses of the model and the real cone cell were in good agreement for 10 millisecond flashes and 0.7 second steps of light

whose intensities ranged over 2.5 log units with the intensity of the unattenuated light at 1.5×10^{17} photons per second per square centimeter.

An operating system for the MAC-16 system has been developed which provides the user with easy access to compilers and major programs, handles I/O for all peripheral devices, and automatically allocates system facilities and storage during execution of user programs. For example, a program for A/D conversion of dynamic pulmonary compliance data was assembled using this new operating system (see Section on Pulmonary Pathophysiology and Respiratory Disease).

The Medical Neurology Branch, NINCDS is studying the use of electromyograms to determine muscle fiber conduction velocities and to investigate disease states. Preliminary analog to digital conversion and spectrum analysis has been performed on the data, to define the filtering and amplification requirements of the data collection.

The Division Cardio-Renal Drug Products, FDA is investigating the early detection of cardiac toxicity resulting from drug therapy. Electrocardiograms are being used to determine the sensitivity of detection. Programs have been written and preliminary analog to digital conversion of the data has been done to provide data for the analysis programs.

Significance:

The hardware simulation effort has continued to make available to the physiologic researcher cost effective ways to investigate and help teach basic cellular behavior.

Currently the effect on cardiac behavior of various drugs, in particular, cancer chemotherapy agents, is monitored by a single lead electrocardiogram (ECG) in animals. The end point for cardiac toxicity is terminal ventricular tachycardia. The current study is investigating multiple lead ECG's and the computer analysis of this data to provide a more sensitive and accurate end-points for drug effects.

Proposed Course:

The operating system for the MAC-16 will be upgraded for user ease. The EMG study will be continued with emphasis on attempting diseases states, and additional analysis programs will be written for the drug detection study.

Publications and Abstracts:

Covacci, Renato: Techniques for the hardware simulation of the turtle cone photo responses and extensions of the validity of the

model to the salamander cone, Proceed del Gruppo Nazionaledi Cibernetica e Biofisica, Piza (Italy), (in press).

Vallerga, S. Covacci, R., and Pottala, E.: Hardware model of turtle cone photo responses, Proceed del Gruppo Nazionaledi Cibernetica e Biofisica, Piza (Italy), (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00042-01 LAS

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Computer Based Analysis and Image Processing in Electron Microscopy and X-ray and Electron-Loss Spectroscopy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.W. Pottala	Elec. Engineer	LAS	DCRT
	J.L. Costa	Medical Officer	CN	NIMH
	C.R. Swyt	Physicist	EA	NHLBI
	C.E. Fiori	Physical Scientist	BEIB	DDR
OTHERS:	M.A. Douglas	Computer Systems Analyst	LAS	DCRT
	K.E. Gorlen	Elec. Eng.	CSL	DCRT
	C.R. Creveling	Chief	LC	NIAMDD
	E. Silbergeld	Chief, Neurotox. Sect.	LP	NINCDS

COOPERATING UNITS (if any)
Biomedical Engineering and Instrumentation Branch, DRR, Computer Systems Laboratory, DCRT, Clinical Neuropharmacology Branch, NIMH Laboratory of Chemistry, NIAMDD, Laboratory of Experimental Atherosclerosis, NHLBI, Section on Neurotoxicology, NINCDS

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

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DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.1	2.0	.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves collaboration of LAS with BEIB and several NIH Institutes. It is directed toward the development of computer-based mathematical and statistical analyses, pattern recognition, and image processing of data, principally X-rays and electron energy loss spectra, derived from biological specimens studied in an analytical electron microscope.

Background and Objectives:

BEIB has purchased a 200 kilovolt scanning transmission electron microscope which can produce both pointwise spectral data (electron energy loss, X-ray) and matrix images containing spectral information. It is connected to a KEVEX 7000 spectrometer and with various other hardware interfacing to a DEC 11-60 computer system. The basic hardware configuration and systems software is being developed by CSL along with subroutines to store data and perform arithmetic manipulations on various types of images (i.e. to perform background corrections and to compare images of mass density present in a specimen with those reflecting the distribution of specific elements).

BEIB has planned this research facility in collaboration with NIMH, NHLBI, NIAMDD, NINCDS, and DCRT to develop pioneering applications of analytical electron microscopy. This can be accomplished because:

1. The high energy beam (200Kev) will provide a significant increase in the signal-to-noise ratios of the chemical information and should make possible the analysis of hydrated specimens.

2. The assemblage of hardware and computer systems allows rapid data acquisition and the complex processing necessary to extract chemical information from the raw data - both heretofore unavailable at other installations.

Of particular interest are the electron-energy loss spectra (inelastically scattered electrons) which contain information about the chemical composition of the specimen, the back-scattered electrons, and the elastically scattered electrons (both related to the mass density of various specimen regions). The physics of these various types of electrons as well as the measured specimen current and secondary electrons emitted needs to be elucidated in order to formulate the proper mathematical or statistical models which can combine this information into a "true" or corrected elemental map on a pixel-by-pixel basis. These models will likely account for contributions of neighboring pixels as well as a Poisson process in some cases. The relationship between elemental (energy-loss) peaks, zero-loss (transmission) peaks, and the plasmon peaks as well as the background contribution requires further exploration and quantification.

The potential resolution for chemical analyses of the system is in the range of 10^{-6} to 10^{-20} gms. and the spatial resolution is in the order of 100 - 1000 square Angstroms. In addition the system can

construct maps of 1024 x 1024 pixels. Clearly, the further development of this tool will require a new kind of image processing which will differ radically from the usual sort applied to nuclear medicine, X-ray devices, and ultrasound.

Progress During FY 79:

The main event was the arrival of the equipment - the microscope, the spectrometer, hardware, and computer. The set-up of the hardware and basic systems software is expected to be completed near the end of FY 79.

Significance:

The ultimate biological goal is to relate structure and function at the ultramicroscopic, molecular, and chemical levels. Certain active molecules - e.g. enzymes, neurotransmitters, hormones, antibodies, etc - can be tagged with appropriate labels - e.g. fluorine - and then localized and quantitated within cells by means of this tool. It should be possible to determine as well the distribution of double bonds within membranes, microtubules, and cytoplasmic organelles. The distribution of elements of great biological importance - viz. calcium, magnesium, nitrogen, sulfur, and oxygen - can also be determined.

Thus, the research potential of this tool has widespread applications in all areas of biology concerned with ultrastructure, much as the development of the imaging capability of the electron microscope itself has provided important insights in almost every area of biology.

Proposed Course:

The study of the basic physics and the formulation of appropriate mathematical/statistical models needed to achieve the analytical capabilities will require extensive work with phantoms, i.e. specimens prepared by such means as vacuum evaporation, which are very thin and of known composition. There will need to be extensive studies of the signal/noise ratio in phantoms and in biological specimens. Potential problems with contamination and with specimen destruction by the high energy beam also need to be studied. Sophisticated algorithms for element recognition and location, image enhancement, etc. need to be designed and, where practicable, implemented on the DEC 11-60 system for rapid turnaround.

LAS proposes to undertake, in collaboration with BEIB and the other participating Institutes, some of these objectives after the combined system is operational.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00006-09 LAS

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Generalized Mathematical and Computational Methods

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. Hill	Computer Systems Analyst	LAS	DCRT
OTHER:	R. Shrager	Mathematician (formerly LSM, DCRT)	LAS	DCRT
	J. Fletcher	Chief, AMS	LAS	DCRT

COOPERATING UNITS (if any)
none

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.4	.4	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The work under this project has been in two general areas: 1) generalized optimization techniques for data fitting in the L-one and L-infinity norms using the Simplex Method; and 2) file migration modeling using optimum network flows in the evaluation of computer system performance. In the first area, curve fitting methodology utilizing the Levenberg-Marquardt Method for fitting Non-linear Models have been implemented as a general Modeling system called an Optimization Laboratory (OLAB). Constrained methods are being developed that will contain the unconstrained methods as a subset. After completion of formulation and testing of the constrained methods the unconstrained methods will be replaced by the new constrained methods. The second project area involves the analysis of computer systems performance. A methodology for evaluating computer system performance has been formulated and described.

Background and Objectives:

The project on optimization techniques and data fitting is concerned with the development of two areas of computer applications and mathematics in the biosciences. The first area is concerned with nonlinear model fitting and parameter estimation. The "standard" methods of least squares have been extensively developed for fitting nonlinear models to experimentally obtained data with estimation of unknown parameters in these models as a basic objective. For many applications, the least squares criteron is not appropriate and may introduce unnecessary computational difficulties. For example, fitting data taken over a wide range of values of the independent variables, and fitted without weights, tends to bias the results toward the data associated with larger values of the independent variables. The problems of ill-conditioning with systems having several parameters are also well known. Until recently, methods for fitting models with nonlinear parameters were not available with other than the least squares criteria. This project was concerned with the development of such new criteria.

These methods have been embedded in a generalized modeling system called a Mathematical Modeling Laboratory (MLAB). The new modeling system is called an Optimization Laboratory (OLAB). Currently, OLAB is running using unconstrained algorithms. Ideally, the bioscientist would like the capability to constrain the parameters in his models to insure that the models are realistic. A constraint algorithm is under development to allow the bioscientist to fit models with the parameters both unconstrained and with constraints.

The project concerned with evaluating performance of computer systems deals with the development of algorithms for optimum file migration, and computer system benchmarks. The file migration area of research was initiated because of the increase in the number of magnetic tapes containing migrated files. The benchmark scheme is a method designed to analyze computer system data. This method was proposed to assist management in the evaluation of the performance of a computer system based on the past history of the system.

Significance for Biomedical Research:

Data fitting offers the biomedical scientist a methodology of determining unknown parameters in biological models. After a model has been formulated these techniques are used with laboratory or clinical data to study parametric relationships in the model.

The file migration algorithm is designed to reduce the number of files at certain levels in the computer system. Development of a good benchmark is essential for use when the system is being analyzed for updating or replacement. These techniques can directly reduce the cost of biomedical research by reducing the space to store files and aiding management in the evaluation of computer system performance.

Progress in FY 79:

In FY 79 the Levenberg-Marquardt Method for Nonlinear curve-fitting in the L-one Norm and L-infinity Norm have been embedded in a generalized modeling system called MLAB which is implemented on the NIH PDP 10 computer. Articles describing these methods and some applications have been published. The interactive computer systems are now available as general research tools, and seminars describing their use have been given.

A file migration algorithm has been formulated using network theory. A benchmark scheme has been developed for use when setting up a benchmark for computer system performance evaluation. Articles describing this work have been published.

Proposed Course:

New constraint algorithms will be implemented in OLAB as they are developed and tested. Further work on the evaluation of computer performance will be subject to section priorities.

Publications and Abstracts:

Hill, E.: Discrete rational approximation in the L-one and L-infinity Norms using the Simplex Method, Proceedings of ACM 1978, December 1978.

Hill, E.: Attributes of a file migration model for shared files, ACM Computer Science Conference, February 1979.

Hill E.: Computer systems evaluation, Conference on Information Sciences and Systems, The Johns Hopkins University, Electrical Engineering Department, March 1979.

Shrager, R. and Hill, E.: Some properties of the Levenberg method in the L-one and L-infinity norms. Mathematics of Computation (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT00045-01 LAS

PERIOD COVERED
October 1, 1978 to September 1, 1979

TITLE OF PROJECT (80 characters or less)
Numerical Approximation Techniques for the Solution of Reaction - Diffusion Systems in Biology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Bieterman	Mathematician, AMS	LAS	DCRT
OTHER:	J.E. Fletcher	Chief, AMS	LAS	DCRT
	B. Bunow	Biomathematician, AMS	LAS	DCRT
	I. Babuska	Professor, Institute of Physical Science and Technology Univ. of Maryland		

COOPERATING UNITS (if any)
none

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.9	.9	

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The fundamental tools needed to compute the solution of model reaction-diffusion systems are the mathematical techniques and related software used to solve nonlinearly coupled partial differential equations via computer. This project provides two interrelated forms of mathematical support for ongoing laboratory modeling of biological processes: (1) new, theoretically sound and computationally efficient numerical solution techniques are investigated and developed into computer programs, and (2) existing methods and computer programs are modified and implemented to solve specific models.

Background:

The mathematical models describing reaction, diffusion, and transport processes in biological and physicochemical systems consist of systems of nonlinearly coupled ordinary and partial differential equations. Specific mathematical techniques and numerical methods needed to treat many of those equations either do not exist in the present literature, or require a very large amount of computer time, making their implementation economically impractical. The development of new techniques, and continuing attempts to improve the efficiency of known algorithms are the objectives of this research area.

Significance to Biomedical Research:

The types of equations being studied are used to model substrate transport in the mircrocirculation and embryologic pattern formation. Other biomedical application areas include population dynamics of ecological systems, population genetics, nerve impulse transmission, and tumor growth, vascularization, and necrosis. The effective modeling of physiologic processes requires efficient methods for the numerical solution of systems of lumped or distributed parameter models. Such models are required to describe the complex interacting systems with flow, diffusion, and chemical reaction which are basic to normal and pathophysiology. Collection and characterization of solution techniques also makes them available to the NIH biomedical community as research tools.

Progress in FY 79

Investigation of numerical methods used to solve coupled systems of linear and nonlinear partial differential equations has continued. The methods include both finite difference techniques and finite element methods. Previously written software was upgraded, and a number of new computer programs were added to our library.

In the area of microcirculation modeling, finite difference schemes are being developed to solve a model which incorporates time dependent capillary transport effects.

Versions of the Bathe-Wilson finite element code were implemented on the NIH IBM 370 system. The programs were modified to solve time dependent, steady state, and eigenvalue problems associated with biological pattern formation on irregularly shaped, two dimensional regions. The flexibility provided the user in description and discretization of regions, solution accuracy obtained, and speed of computation show the finite element method to be a useful and productive tool in biological modeling.

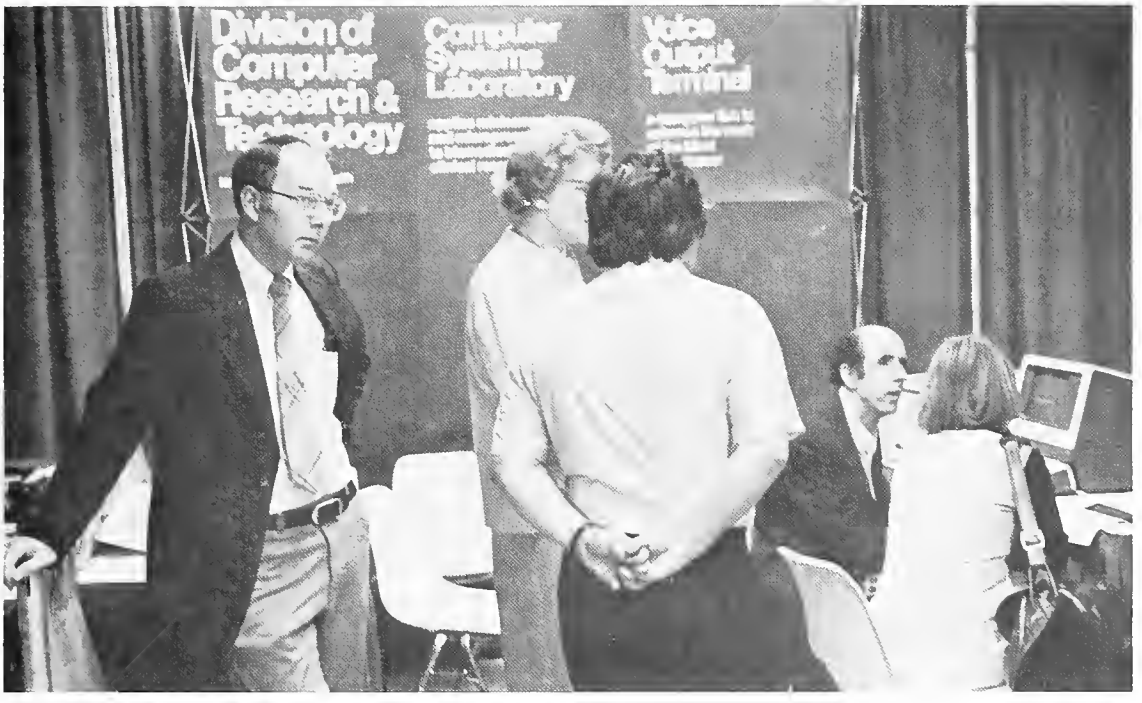
Background studies and initial research have been completed for the development of adaptive finite element schemes for the solution of time dependent reaction-diffusion systems. The schemes are adaptive in that a temporal and spatial mesh refinement strategy, based on reliable, local a posteriori error estimates, is carried out by the computer during the problem solution. This procedure is expected to minimize required computer time, especially for models involving the response of systems in a nonuniform medium, on which attention is focussed.

Proposed Course:

Mathematical support of ongoing modeling projects will continue in the forms into research of adaptive finite element and finite difference schemes and further development and application of known techniques to specific models. These efforts will continue at levels determined by section priorities and manpower.

COMPUTER SYSTEMS LABORATORY

Alan M. Demmerle
Chief



Using technology originally designed for medical telecommunications projects, CSL members implemented a voice output terminal for blind computer programmers. Exhibiting the terminal at the 1979 President's Conference on the Employment of the Handicapped, Perry Plexico (left) and David Songco (back to camera) answer questions.

I. SUMMARY

Function

The Computer Systems Laboratory (CSL) identifies and solves problems in areas of biomedical research and clinical care where real-time data collection, analysis, display and experiment control are required, where economic considerations favor a small computer, or where proximity of the computing equipment to the work site is important to successful solution.

CSL's approach to each project varies as each problem presents unique challenges. The staff:

- analyzes the users specific requirements.
- evaluates alternative solutions with regard to technical merit, time to completion, and cost.
- discovers new solutions to automation problems.
- develops special components to meet user's needs.
- refines systems to adapt to research progress.

The activities of CSL center in these principal areas: applications in a clinical environment, applications in laboratory research, and consultation with researchers in need of computer expertise. These activities are carried on with approximately 30 employees, two-thirds of whom are electronic engineers, and the remainder computer scientists with diverse backgrounds including some with backgrounds in medicine, biology, and chemistry.

Scope of Work

Over the past ten years, CSL has worked with nearly all of the Institutes on a wide variety of requirements. Major effort has been expended upon a few large projects that have required an investment of ten to twenty-five man-years. In fact, some of these long-term projects have no distinct ending because of continuing modification to accommodate new research protocols.

Most of the projects this year were started in earlier years, or in some cases grew out of projects started earlier. One significant factor affecting the ratio of old to new projects is the decreasing size of our Laboratory. As the number of personnel decreases the progress on existing projects slows and we are seriously restricted in our ability to start new projects.

Each year, CSL also has a number of relatively small jobs, ranging in size from one man-week to a half man-year. These involve consulting with the intramural and extramural programs in the areas of automated data collection, display and analysis, data transmission, certain

aspects of biomedical sensor design and all aspects of real-time computer system design.

Intramural consultation often is followed by development of hardware and software systems; extramural consultation activities are primarily advisory. The consulting activities are valuable to us in that they help keep us aware of other activities in biomedical engineering, but require only a minimal commitment of manpower resources.

Highlights of the Year's Activities

During FY79, CSL continued to utilize minicomputer and microcomputer based technology in support of clinical care and laboratory research programs of widely varying scope and duration. Three projects of recent origin are clinically oriented but nevertheless reflect much of the diversity of CSL work and fully illustrate the impact of CSL contributions to the biomedical community.

The Cardiac Scintillation Probe Project illustrates CSL's commitment to identifying and implementing new applications of computers to clinical research at the NIH. It also indicates the impact that the new and still emerging microprocessor technology is having on biomedical instrumentation.

This pioneering effort began in FY77 as a spin-off of a large, elaborate diagnostic system developed at NIH several years ago. That system combines a scintigraphic camera, a computer, a display, and other equipment to analyze heart function. Whereas the camera system is large and not easily moved, the Cardiac Scintillation Probe was developed to provide a direct, quick, and noninvasive means of measuring left ventricular (LV) function. These attributes offer a physician the potential, at the bedside, for examining acutely ill patients prospectively for predictors of a worsening condition.

The instrument consists of a scintillation probe on an adjustable arm affixed to a cart that can be easily positioned at the bedside. The cart contains probe electronics and a microcomputer. The instrument is used to acquire scintillation data by positioning the probe over the left ventricle (LV) of a patient who has been injected with an appropriate radioisotope. The microcomputer program organizes these data into a composite LV time-activity curve, corrects the curve for the effects of background radiation, and calculates ejection fraction, an important measure of cardiac performance. Both the time-activity curve, which is proportioned to LV volume, and the calculated ejection fraction are displayed in real-time.

During the current year, the instrument was further developed for use in NHLBI's cardiac catheterization laboratory. It is used, in conjunction with LV catheterization, for simultaneous LV volume and pressure determinations. LV pressure-volume measurements can be made in real-time so that pressure-volume loops and other displays can be

generated, and parameters such as LV compliance can be determined while a patient is still in the laboratory. The advantages of this method, compared to conventional approaches, are striking. For example, LV volume determinations resulting from measurements made on cineangiographic films of the heart can normally be obtained only hours or days following the catheterization procedure.

Current work includes the development of methods for making background corrections simultaneously with LV volume measurements. We also plan to develop a new high efficiency probe which will allow statistically reliable measurements in much less time than is currently required. It will also enable beat-to-beat evaluation of LV volume, something which is not now possible.

The Medical Intensive Care Unit Patient Monitoring Project involves automated collection, analysis and display of data from the recently established Medical Intensive Care Unit (MICU). This unit is administered by the newly formed Department of Critical Care Medicine in the NIH Clinical Center and receives critically ill patients from clinical programs of NIH. The MICU comprises a 5-bed ward area, a 2-bed special study area, a pair of isolation beds, and a vascular research laboratory.

The primary objective of the Project is to combine continuous automated data logging of patient vital signs (including respiratory functions) with vascular catheterization data. The MICU goals require the use of three minicomputers and a microprocessor.

The bedside patient monitoring system consists of Hewlett-Packard physiological monitoring components at the bedside and a central Hewlett-Packard minicomputer system. Bedside 16-button keyboards and 12-inch CRT displays allow the medical staff to interact with the computerized monitoring system. Terminals located at the nurses' station and at three other convenient sites provide for the entry of textual information, as well as control and display of data.

The physiologic signals to be monitored include heart rate; systemic arterial, pulmonary arterial, and pleural pressures; body temperature; urine output; respiration rate; airway pressure; and airway flow.

A second Hewlett-Packard minicomputer provides for data acquisition and subsequent data processing within the vascular research laboratory. A physiologic monitoring console containing eight signal conditioners, an eight channel oscilloscope, an eight channel strip chart recorder, and a seven channel analog tape recorder will be used to acquire physiologic data during pulmonary vascular and peripheral vascular catheterization procedures. On-line data collection and analysis is controlled from within the catheterization laboratory using a specially designed keyboard and a CRT display. This system is magnetic tape compatible with the bedside monitoring system.

Program development for above described computer systems will be accomplished with a third Hewlett-Packard minicomputer. This program development system will also support data base management software.

Pulmonary gas exchange will be evaluated through the use of a Cemetron medical mass spectrometer permanently located in the computer room. The mass spectrometer's inlet line is connected to each patient's airway by means of electronically controlled solenoid valve leading from a common gas manifold. Long small-bore tubing runs from each solenoid valve to a T-adapter on the respirator's delivery tubing.

Data from this mass spectrometer will be interfaced to the Hewlett-Packard data management system, in order to merge pulmonary function and gas composition data with the main patient data files. In addition, the incorporation of airway pressure and flow monitoring into the Hewlett-Packard systems, through modifications to be installed by CSL staff, will allow the computation of net O_2 consumption and CO_2 production values.

The final components to be added to the commercial patient monitoring and data management system are IMED computer-controlled volumetric infusion pumps. Integral microprocessors allow these infusion pumps to engage in two-way communication with the monitoring system. Carefully developed and well-proven algorithms for continuous intravenous infusion therapy will provide rate control of these infusion pumps, based on the values of the physiologic parameters to be controlled.

The Biomedical Image Analysis Project is expected to provide an image analysis capability appropriate to a wide-range of CSL activities and NIH requirements.

This project had its origins in the Computerized Radiotherapy project which seeks to use computerized tomography (CT) images to calculate better radio therapy protocols. The Biomedical Image Analysis Project has taken advantage of the powerful DCRT Evans and Sutherland (E and S) Image System to develop, and test the suitability of algorithms to achieve improved organ and tumor identification and contouring. The algorithms include both classical and experimental techniques for producing contrast enhancement, edge detection, contour extraction, contour following, contour coordinate data compression and three-dimensional representation. While many of these algorithms achieve improvement over currently existing clinical techniques, the approaches considered to be the most promising use discriminating features derived a priori from large populations of data representing normal and diseased organs.

The image analysis effort on CT scans attracted the interest of scientists engaged in other research programs. Two projects, an NHLBI atherosclerosis study and an NINCDS neuro-anatomy modeling project, evolved from this interest during the past year.

Investigators in the Laboratory of Experimental Atherosclerosis, NHLBI study the topological variation of disease along arteries of experimental animals fed high cholesterol diets. The arterial segments are removed, opened, pinned out, stained, and photographed.

CSL was asked to provide a way for determining statistical measures of the disease involvement from the pictures of these sections. We developed algorithms to normalize sections by mapping them into standard templates and to extract areas of disease involvement as well as total section area. These programs are now operational.

Investigators in the Laboratory of Neuro-Otolaryngology, NINCDS, asked CSL to collaborate on techniques to visually explore the anatomy of the auditory system of the mammalian brainstems. Data representing neuronal cells and their spatial relations in one superior olivary complex of a cat brain were derived manually from sections of the complex.

These data were transferred to the DCRT E&S System via magnetic tape and intercomputer transmission and transformed and displayed in color, each color representing a particular class of neurons. The primary display for each section was composed of small colored squares each representing the neurons counted in an 80 micron square area. Next software was developed to interpret all the data as stacked planes of 80 micron colored cubes and to view any arbitrary planar slice through this block model. Images generated by the block model may be transferred back to a local Neuro-Otolaryngology Laboratory computer for printout on their Versatec plotter.

A 16mm color movie entitled "Atlas of the Cat Superior Olivary Complex" was produced. This movie shows the computer generated images representing the original 61 sequential transverse sections followed by sequential reconstructed images representing horizontal and para-sagittal sections.

Users of the block model feel it provides insight into the anatomy of the superior olivary complex. We planned to improve and extend the usefulness of the model as a research tool.

Future Plans

Our future depends upon our ability to maintain our size, and meet the challenge of wisely setting priorities in an environment of increasing demand for our serivces. For the past several years, CSL has suffered personnel cuts, and FY79 is no exception. These recent cuts emphasizes the problem of setting priorities in the work we do; in selecting from among the new projects presented to us, and the continuation of old ones.

Perhaps, the most difficult choices to be made concern the level of effort required to support some of our projects. The timing of completion of our projects is often critical; delays reduce the value

of a project. In essence, our projects are timed to the interests of the scientists we support, and to the activities of the instrumentation industry. If we are too slow the scientists move on to other work and we fall behind the fore-front of technology. In addition the "critical mass" concept applies to some of our larger projects where a number of people, representing several specialities are required.

Thus, the priorities cannot always be established only on a deliberate assessment of value of the project. It must take into account other factors including available talent, previous commitment, project size, and timing constraints.

- Clinical Research, Patient Care Projects

Computerized Radiation Therapy, NCI, RO: CSL, in collaboration with the Radiation Oncology Branch, NCI, has developed a computer system now in operation in R.O. to use the detailed contour and density information available from computer assisted tomography to improve radiation treatment planning. Our system allows the radiotherapist to review scans of a tumor area at a video terminal.

The therapist may quickly vary the presentation of the image to emphasize a particular structure, or magnify an interesting feature. Outlines of the tumor or vital organs, in some cases drawn automatically by the computer, are then processed by software algorithms procured from Atomic Energy of Canada, Ltd. to provide sophisticated individualized treatment plans. Finally, the calculated dose distribution may be overlayed on the scan for evaluation of the plan.

During the past year, CSL has added improved display hardware to the computer system, and written a large collection of programs to allow display and manipulation of both grey-scale and true color images of the scans. Also, programs were written to permit manipulation of the displayed scans (sector selection, magnification, zooming, etc.), to computer designated areas and distances, and to aid the therapist in planning treatment. For example, it is now possible to display lines of isodose in unique colors, overlayed on the original CT scan. A large, much faster disc was added to the system to accomodate the large amount of data generated by clinical usage.

Current development includes calculation of dose off the central beam axis along the third dimension of the tumor, an investigation of ultrasound as an instrument for treatment planning, psuedo-optimization of treatment planning, and procurement of tumor registry software.

Medical Intensive Care Unit Patient Monitoring Computer System, CC, DCCM: During this reporting year, a five-year contract was initiated with the Hewlett-Packard Corporation for the acquisition of a commercially developed computerized patient monitoring system for the Clinical Center's new Medical Intensive Care Unit. The monitoring system's primary function will be the periodic data logging of vital signs from the nine bed care unit.

A separately procured medical mass spectrometer, with an attached microcomputer, will provide the patient monitoring computer with information on respiratory gas composition. Pulmonary vascular studies will be carried out using a computerized vascular research subsystem, and a development computer subsystem will allow the testing of new applications programs in support of ongoing research protocols and will provide for data-base management.

The monitoring system's installation requirements were identified and the Medical Intensive Care Unit's construction specifications were modified appropriately to ensure compatibility. Construction of the new care unit proceeded as the computerized monitoring system arrived. Following completion of the care unit, installation of the computer system was initiated and the first patients were admitted to the unit a week later as the bedside monitoring equipment became functional.

A survey of commercially available intravenous infusion pumps was carried out in order to choose a pump for interconnection to the computerized monitoring system. A pump was selected containing an integral microprocessor that allows bi-directional communication with the monitoring system.

CSL expects continued involvement during the forthcoming year.

Cardiac Intensive Care Unit Patient Monitoring Computer System, NHLBI, SU: For the past several years CSLand S.U. of NHLBI have been collaborating in the development of a system to collect, format and display vital data from post surgical cardiac patients. The annual report from previous years elaborates on the goals and characteristics of this system. This year a particularly significant accomplishment has been the acceptance of computer output, by the NIH Medical Records Committee, for inclusion into the permanent patient chart. Also this year an alarm generating software package, which produces messages when monitored parameters exceed preset limits, or when certain abnormalities in the parameters are detected, was completed. Future plans include a formal evaluation of the operation of this system and study of a next generation system for implementation in new NHLBI care facilities. A reduced level of effort is anticipated during the coming year.

Computer Systems for Nuclear Medicine (Previously Reported as Cardiac Scintillation Probe), CC, NM and NHLBI, IR CB: CSL has continued development of its Cardiac Scintillation Probe System begun in 1977. This non-imaging ECG-gated scintillation probe, when used in conjunction with left ventricular (LV) catheterization, permits simultaneous quantification of the variation of LV volume and pressure. It combines a new high efficiency scintillation probe with computerized data acquisition, processing, and display to produce a time-activity curve in real-time. When the probe is properly positioned over the left ventricle, this time-activity curve is a measure of change in LV volume. By simultaneously measuring LV activity and LV pressure, parameters such as LV compliance can be continuously monitored. This year we implemented the capability for performing real-time pressure-volume measurements in the cardiac catheterization laboratory for drug intervention studies. These results were presented to the Nuclear Medicine Society in June 1979. During the coming year, we expect to achieve further increases in probe efficiency so as to permit beat-to-beat analysis of ventricular function.

We have also continued our consultation and support for the imaging systems located in the Nuclear Medicine Department. This involved assessing computer requirements with respect to the continuing increase in the number of clinical and research studies. This year we began working toward a distributed processing system (DS) in Nuclear Medicine by inter-connecting two imaging systems. During the coming year, the DS system will be expanded so that all imaging systems are connected together in a network. For relatively little expense, the DS system increases the capabilities and utilization of diagnostic imaging by allowing peripherals to be shared and minimizing scheduling conflicts. We are also collaborating with Nuclear Medicine and the Cardiology Branch is purchasing and implementing a portable scintigraphic camera and associated computerized imaging system for use in Cardiology's animal laboratory.

Automated ECG Processing, CC and NHLBI, IR CB: The Clinical Center's ECG Service requested assistance in 1977 in specifying and acquiring an on-line ECG system to assist staff physicians in analyzing and reporting current ECG's and comparing serial ECG's. CSL and LAS have reviewed available literature, field tested commercial systems, and followed DOD's Tri-Service Medical Information System procurement effort. A system was specified in 1978 but procurement was postponed by the Clinical Center. The 1978 draft request for proposals (RFP) containing functional specifications for a minicomputer-based ECG system was revised and upgraded in 1979 to include, among other things, greater emphasis on research data processing and interchange of ECG tracings and reports. The RFP is currently awaiting action by the Research Contracts Branch; funding of the system is expected to be accomplished with FY79 or FY80 money.

Pulmonary Branch Project, NHLBI IR: The Pulmonary Branch of the National Heart, Lung and Blood Institute has asked that CSL participate in an intensive collaboration with two primary goals:

1. Automation of the various test procedures performed by PB, thereby obtaining increased accuracy and faster turnaround from test performance to useful clinical results.

2. Development of a patient database for storage and retrieval of all test results generated by PB such that they can subsequently be used to follow an individual patient, or to evaluate the potential clinical significance of findings across patient populations.

This project is anticipated to be a significant and time-consuming endeavor, requiring CSL manpower resources that are not available at this time. An effort to recruit a special expert who will work in this area for the anticipated project duration of two to three years is now underway. In the meantime, CSL is providing limited consultation to PB to ensure that equipment procurements and data processing steps taken now will be consistent with future needs.

Clinical Pathology Department Project, CC: A general-purpose microprocessor-based instrument interface is being developed in conjunction with the Clinical Pathology Department, CC. The intent of this project is to link a variety of analytical instruments to the Clinical Pathology computer in a similar fashion. This will include the interfacing of instruments not previously connected to the computer, as well as the replacement of some existing interfaces. The new interfaces provide the means of processing specimens independently of predetermined load lists, local preprocessing and edit checking of data prior to transmission to the computer, and a mechanism for rapid certification of results for priority (stat) requests. These enhancements were not possible with the existing techniques.

A prototype unit has been implemented for a Coulter Counter, an instrument which analyzes blood for seven different parameters. This device was installed and placed in operation in May 1979. Additional units are planned for a second Coulter Counter, a blood gas analyzer, and a Technicon SMAC automatic analyzer.

Biomedical Image Analysis, NCI, RO and CC, DR, and NHLBI, IR and NINCDS, LNO: During the past year, CSL has participated in several collaborative intermural biomedical research projects having image digitization, transmission, storage, retrieval, processing and analysis as common requirements. The DCRT Evans and Sutherland Picture System (E&S) has been serving as the host computer in this work. We are working toward making a "utility" for picture processing which currently features: 1) tape compatibility between EMI CAT Scanners and the DCRT (E&S) System, 2) tape compatibility between an Optronics densitometer (located at Johns Hopkins University, used by NHLBI) and the DCRT E&S System, 3) a library of image processing and analysis software, much of which is interactive, 4) a 16mm color movie facility for documenting colored 3-dimensional displays.

Progress in specific collaborative intermural projects is reported below:

Members of the Laboratory of Experimental Atherosclerosis, NHLBI are studying the topological variation of disease along the arterial tree of animal specimens. Images of stained arterial sections taken from various experimental animals are currently digitized by means of a microdensitometer for input to the DCRT E&S System. The images are mapped into standard templates and the area of disease involvement is determined. Most of the processing software is operational and current efforts are directed toward digitizing, processing, analyzing, and presenting results related to approximately 400 images.

The Laboratory of Neuo-Otolaryngology, NINCDS has requested the development of a 3-dimensional block model of the cat brain stem from which 2-dimensional images and shaded surface drawings representing any chosen plane may be reconstructed. The block model is now operational and a 16mm color movie illustrating its use has been produced.

In collaboration with the Radiation Oncology Branch, NCI and Diagnostic Radiology, CC, several programs have been written to improve upon the use of CAT scan data in radiation treatment and diagnostic procedures. These programs, most of which are interactive include contrast enhancement, edge detection, edge extraction, data compression and 3-dimensional reconstructions.

We expect to continue work, possibly at a reduced level of effort, during the coming year.

Flow Microfluorometry Cell Sorter (FMF), NCI, I, LP and NIAID, LMI: Since FY75 CSL has provided engineering, system integration, and software support necessary to meet the data acquisition, data display and analysis needs of investigators using Flow Microfluorometers (FMF's) at NIH.

In FY77, the popularity of cell analysis using the shared computer based NCI FMF system increased considerably with the result that the existing computer system could no longer handle the workload. In April 1978, the installation of a second computer (PDP-11/34) provided each of the two NCI FMF instruments a dedicated computer. Also in FY78, major emphasis was placed on improving existing and implementing new support software. Some of the display and analysis programs have been enhanced to reduce the time spent by researchers at the computer console by providing automatic sequencing through data files. This feature is accomplished by preselection of parameters that are automatically applied to one or more data files without operator intervention.

New statistical calculations were added in FY79. Also, a large part of a comprehensive user's manual was written to provide operating and installation instructions for CSL written software, and to facilitate effective use of the computer in the FMF environment.

A PDP-11/34 system that was ordered in April 1978 by NIAID, IMI, was delivered in December 1978. A contract was awarded to a commercial vendor to fabricate from CSL plans a FACS II/PDP-11 interface for the NIAID system. Because of room renovation delays and modifications to the FACS II FMF, the NIAID FACS II instrument-computer system has not yet been integrated although most of the software has been successfully tested on the PDP-11/34 system.

Evaluation of existing and anticipated requirements for the two FACS FMF systems has resulted in CSL recommending that software currently running under the RT-11M single user operating system undergo conversion to function under the RSX-11M real-time multiprogramming operating system. Planning for this conversion is already underway. We also recommended replacement of the NCI PDP-11/40 computer with PDP-11/34 and additional memory and data storage capabilities. Currently, we are also working on minor improvements to the applications program (under RT-11) for LASL, the second NCI FMF system.

The NIAID FACS system has the recommended equipment for the software conversion. CSL expects to convert the existing application programs for FACS, and to design and implement under RSX-11M a more sophisticated data acquisition program that will allow considerable record keeping to be done by the computer rather than the experimenter.

In the forthcoming year, CSL plans to continue adding automatic sequencing capabilities to the display and analysis programs, complete the User's Manual and begin implementation of RSX-11M software.

- Laboratory Investigation Projects

Distributed Laboratory Data Acquisition and Control System, NIAMDD: A Distributed Laboratory Data Acquisition and Control System (DLDACS) is being implemented for NIAMDD, in Building 2, as a replacement to the Laboratory Computer System developed here in CSL ten years ago and which has now become overloaded and technologically obsolete. The new system will consist of a network of remote microcomputers connected in a star configuration through a communications processor to a central data processing computer. The remote microcomputer handles all of the real-time data acquisition requirements and provides instrument control functions when required. The collected data is normalized, buffered and transmitted at a convenient time to the communications processor as files over a serial line, using a standard block communications protocol. The communications processor serves as a store and forward front end for the central computer. Utilizing serial multiplex hardware, it is capable of communication with up to twelve remote microcomputers and places incoming files on a queue to be transferred over a parallel DMA channel to the central computer. The new system for data collection and processing is designed to allow laboratories connected to the old system to be converted with minimum disruption to ongoing instrument use.

The prototype element of this network was installed this year. It connects the C-118 Spectrophotometer to the old H-516 computer via the remote microprocessor (DEC LSI-11), using the RT-11 operating system and a communications processor (also a DEC LSI-11).

Much of the software written for this first element in the network can be used for all elements of the network, including that for the communications of data, and for data acquisition. Thus, the remaining elements of this network will require less development time.

Presently, the "central data processing computer" is a Honeywell DDP-516 but in conjunction with the conversion to a distributed system the H-516 will be replaced by a Digital Equipment Corporation PDP-11/70. Major microcomputer components required to convert all laboratories currently serviced by the H-516 to the distributed system have been ordered. Software and interface hardware for two of these units is currently under development. We estimate that six to nine man-months will be required to replace each of the remaining three instruments and we expect to continue working on this project during the coming year.

Scanning Electron Microscope, NIAMDD, LCP and NCI, LP: Following the recommendations of CSL, Drs. Hagins (NIAIDD) and Banfield, NCI, initiated procurement of a combined energy-dispersive (EDS) and wavelength-dispersive (WDS) X-ray analysis system for their scanning electron microscope. A single vendor did not market a combined EDS-WDS system. However, the supplier of the EDS system, Tracor Northern, agreed to integrate their PDP-11/34-based system with a WDS system manufactured by ETEC. The final system will perform analyses as well as acquire and transmit data to the DECsystem-10 for further computation. After a number of delays on the part of the WDS vendor, it now appears that delivery of the entire system is imminent. No further involvement by CSL is anticipated.

Selected Ion Recording gc-ms Data System (Previously Reported as Mass Spectrometer), NIMH, LCS: The SIRS project has been a collaborative effort between the NIMH Laboratory of Clinical Science and CSL to produce a minicomputer based data acquisition and control system for magnetic sector and quadrupole mass spectrometers which would facilitate high volume use of the spectrometers for quantitative analysis and be capable of being modified and enhanced by the user.

Despite signigicant difficulties with the spectrometer, especially in focusing specific ions reliably to within 0.1 mass number, the SIRS data system was completed this year, and is now being used routinely by investigators to perform quantitative analysis with a LKB-9000 gc-ms instrument. SIRS has also been expanded to work with quadrupole spectrometers.

A poster session reporting the availability of SIRS and describing its general characteristics was presented at the Spring Meeting of the American Society for Mass Spectroscopy in Seattle, Washington.

No further work by CSL is planned.

Analytical Ultracentrifuge Data System, NHLBI, IR: Design and development work began in May 1979, on a microcomputer-based data acquisition and communications system for Dr. James Osborne, Jr., Metabolism Branch, NHLBI. This system will facilitate the acquisition and processing of information from an analytical ultracentrifuge and a circular dichroic spectropolarimeter that are the primary tools Dr. Osborne's group use to investigate the interactions between human lipoprotein subunits. Although, the microcomputer system will perform some of the processing, the complex nonlinear analyses necessary for the characterization of interacting systems will be carried out under MLAB on the DECsystem-10. CLINK, the PDP-11/PDP-10 communications software package jointly developed by CSL and CCB, will be used to perform the data transfers.

Microanalysis Facility, BEIB: BEIB is undertaking the establishment of a microanalysis facility which will conduct electron energy-loss spectrometry studies with investigators of several institutes at NIH and NIMH. These studies will involve computer acquisition and processing

of spectral data, investigation of techniques for computer control of the electron microscope, and investigation of some image processing and pattern recognition algorithms.

The facility will consist of two electron microscopes and a PDP-11/60 computer system. The first microscope, a 200 KeV Scanning Transmission Electron Microscope (STEM) was delivered in May 1979, and is equipped with 1) a spectrometer for performing Electron Energy Loss Spectrometry (EELS), 2) a lithium-drifted silicon (Si(Li)) detector for gathering Energy-Dispersive X-ray Spectra (EDS), and 3) detectors for measuring forward-scattered, back-scattered, sample, and secondary electron currents.

The second microscope, a 50 KeV electron microprobe, will also be delivered during 1979. This microscope will also be equipped with a Si(Li) detector and electron current detectors. In addition, it will have three detectors for collecting Wavelength-Dispersive X-ray Spectra (WDS).

The PDP-11/60 computer system, purchased in FY78, will be used to acquire and process data from the two microscopes. The computer system was made operational in April 1979 and a Kevex Model 7000 Analytical Spectrometer was interfaced to it. The Kevex 7000, in conjunction with the 11/60, is capable of gathering and processing spectra from the Si(Li) and EELS detectors on the 200 KeV STEM.

CSL is currently involved in designing and procuring the hardware and software necessary to interface the 11/60 to the 200 KeV STEM. It is planned to equip the 11/60 with a microcomputer-based (LSI-11) front-end processor to acquire the four electron current signals at up to 10,000 samples/second-signal, and also acquire the EELS data and control beam position. All of this data will be transferred to the 11/60 for storage and processing. An Analogics AN5400 data acquisition subsystem has been ordered to permit the 11/60 to control portions of the electron spectrometer and monitor the electron beam voltage, beam current, and lens currents and temperatures.

In conjunction with studies involving wavelength-dispersive x-ray spectra, CSL has been assisting BEIB in developing software for resolving the overlapping peaks which occur in these spectra by using a modification of the Simplex method to optimize the fit of Gaussian functions to the x-ray peaks.

Only the beginning phases of this project have been dealt with to date. It is likely that the data acquisition and control aspects alone will require the contributions of two or three CSL staff members for at least another two years.

Microcomputer-Based Controller for Evoked Response Experiments, NIMH, LBEB: A DEC LSI-11 microcomputer has been configured to operate as a programmable 16 channel pulse generator under the control of an existing laboratory computer system, a PDP 11-40. Prompted by the user, the host

computer, via special communications software, downloads the program and precomputed data files to the microcomputer satellite. The host computer is then free to proceed with data collection and reduction tasks while the satellite controls various aspects of the evoked response experiments. The satellite requires no console, operating system, auxiliary storage or user intervention. Any changes in the timing relationships of the pulses can be effected by the host computer. This project is complete except for final integration of the satellite into the experiment and final documentation. Only minimal effort is expected to be required during the coming year.

Spectrophotometer Data Logger, NIDR: A microprocessor-based data logger was developed to record digital data from a spectrophotometer onto digital cassette tape. Installation of this device was accomplished in July 1979. The user controls the timing and quantity of the sampling, and also the recording of special control blocks via switches associated with the Data Logger. The digital cassette tapes may be played back to NIDR's computer by a commercially procured playback terminal. The format of the tapes is identical to that of cassettes created by other CSL data logging instruments used by NIDR, notably the Radiation Counter Data Recorders, thereby allowing a single cassette tape terminal to be used for playback of data recorded on a variety of CSL developed data loggers.

In conjunction with this project, CSL has been organizing, refining and standardizing a software library and the hardware requirements for collecting data, recording tapes and interfacing to various laboratory instruments (see, for example, Amino Acid Analyzer Data Logger elsewhere in this report).

Amino Acid Analyzer Data Logger, NCI, SURG: During the summer of 1979, CSL developed a data logger that records data from a Beckman amino acid analyzer onto digital cassette tape. The data is formatted in a manner consistent with other CSL data loggers and with commercial playback units. The Data Logger is connected between the amino acid analyzer and its teleprinter and is transparent to both. This instrument includes hardware features and software procedures that have been developed by CSL for other data logging applications such as the Spectrophotometer Data Logger described elsewhere in this report. Those hardware and software elements were developed with special consideration given to the possibility of a variety of future applications.

Radiation Counter Data Recorder (Previously reported as CSL Data Recorder), DCRT, CSL: The Radiation Counter Data Recorder is a device to log data from a rediation counter (liquid scintillation counter, gamma counter, etc.) and write it onto digital magnetic cassette tape. The Data Recorder connects between a radiation counter and its teleprinter and is transparent to both devices. The format of recorded data is suitable for playback to either the DECsystem-10 or the IBM 370 via a commercially available cassette tape data terminal. Over twenty Radiation Counter Data Recorders have been fabricated. Installation of these units in laboratories of NIAID, NICHD, NIDR, NIAMDD, and NCI was

completed early this fiscal year. In anticipation of a continuing demand within the NIH community, a request for proposals (RFP) was prepared this year for outside fabrication and maintenance of the Data Recorders. The RFP is currently awaiting procurement action; initial funding will be in part by CSL and in part by the various laboratories scheduled to receive the initial production quantity of about 25 instruments. Other FY79 activity on this project included the development of test procedures and instrumentation for the contractor to use in testing Data Recorders for quality assurance purposes. Some additional effort will be required during the coming year for monitoring the contract and guiding the installation of new Data Recorders.

NIEHS Computer Facility, NIEHS: The Biometry Branch of the National Institute of Environmental Health Science, located in Research Triangle Park, North Carolina, is responsible for providing computer facilities to meet the needs of the Institute. These needs include scientific and statistical computation, simulation, laboratory data processing, and some business data processing.

In FY78, CSL conducted a study of the current and anticipated future data processing needs of the NIEHS. Based on the recommendations resulting from this study, NIEHS purchased and installed the suggested computer system, which became operational in October 1978. CSL also performed an extensive survey of available telecommunication multiplexors and concentrators which could be used to improve telecommunications access to the DCRT Central Facility by NIEHS, but this solution was abandoned when NIEHS was offered the opportunity to share a telecommunication service that was to be extablished by the Bureau of Health Statistics.

Bioassay Information System, NCI, DCCP; VRB, SAF; FDA, NCTR: The National Cancer Institute has an interagency agreement with the National Center for Toxicological Research for the implementation of NCTR's Research Support System as a computer based information management system for NCI's Bioassay Program. CSL has, since FY77, served as a consultant to NCI in evaluating various specialized hardware and software components of this system, and has provided consultation to NCTR on specifications for microcomputer-based, programmable data acquisition terminals. During FY79, proposals were received from prospective vendors for these terminals in response to a previously issued RFP, and are currently being evaluated. CSL is participating in the evaluation. Ultimately, about 600 of the terminals, representing a value of several million dollars, will be purchased. Over 400 will be used in laboratories doing carcinogenesis testing for NCI.

Closely allied with this effort is an association between CSL and the Small Animal Section of DRS which began this year. The SAS has need for an information management system for its small animal breeding activities, and eventually for supporting long-term animal holding experiments. CSL is assisting DRS staff in evaluating the applicability of the NCTR system to this work. Based on a CSL recommendation, this project was

suspended for the latter half of CY79 pending the outcome of NCTR's terminal procurement and initial testing of the system for NCI.

Laboratory of Immunology System, NIAID: This year, CSL has expanded the capability of a laboratory data acquisition system which we developed several years ago. The improved system provides simultaneous acquisition storage, and processing of instrument data from multiple instruments, as enhanced system has been completed, documented, and operational since December 1978; however, some minor improvements and refinements are expected to be made next year.

Laboratory of Chemical Biology System, NIAMDD: At the request of Dr. C. B. Anfinson of NIAMDD, a peak detecting device for use with a high pressure liquid chromatograph was developed. A microcomputer was used to implement algorithms to detect peaks from the instrument's spectrophotometer output, mark beginnings and ends of peaks on a chart recorder, and control the advance of a fraction collector so that separated material from the chromatographic column may be collected. The unit has been installed and in use since February of 1979.

Potentiometric Titration Controller, NHLBI, IR LC: Work has continued on the microcomputer system for automated electrodic potentiometry. This year the system has been used by the Laboratory of Cell Biology, NHLBI to study the redox potentials of E. Coli cytochromes, resulting in the development of new techniques for the resolving of spectra vs. voltage. A new multi-channel spectrometer has been delivered and is presently being integrated into the system. With this new device under microcomputer control, the time for acquiring complete spectra will be reduced to milliseconds instead of seconds. This is of considerable importance in some experiments because of the rapid change in some parameters and the associated difficulty of maintaining the required experimental conditions. Support for this project is expected to continue during the coming year.

- Biomedical Communications Projects

Computers in Cardiology Conference: CSL has continued its support of the annual International Conference on Computers in Cardiology. The Conference provides a forum for direct interaction and exchange between physicians, computer scientists, and engineers who are involved in various aspects of clinical systems in the field of cardiology. CSL helped plan the 1978 Conference at Stanford University, and edit the Conference Proceedings. Reduced CSL involvement in the 1979 Conference is anticipated, but to date neither the venue of the Conference nor the role of CSL have been determined.

CSL Development System: A PDP-11/70 computer system was purchased in 1978 to be used to support hardware and software development for similar systems with which CSL is involved. This support includes media conversion, cross-generation of operating systems for smaller target

systems, maintenance and development of hardware and software for systems that are unavailable due to their use in production, and prototype computer network software development.

The system was delivered, installed and made operational in October 1978. A second large capacity disk drive which had been previously leased for use on the DCRT DECsystem-10 was purchased and added to the system in March 1979. A communications multiplexor which will permit remote access to the system will be installed later this year, as will an electrostatic printer/plotter, which will be used to support an LSMM project concerned with techniques for presentation of mathematical and statistical information.

Miscellaneous Projects: A limited number of projects engaged in by CSL are not susceptible to classification in the aforementioned categories. Four such projects are reported below:

Library Automation Project, DRS, L: This project was initiated during the current reporting period, in response to a request from the NIH Library to investigate further automation of major library functions. Working closely with the Library staff, CSL has made a thorough study of current activities in the Library to determine those aspects of their operations that could benefit from automation using computers. We then visited several other libraries in various states of automation, interviewed manufacturers of turn-key library automation computer systems and one Bovernment designed system. From this data a report was produced addressing the feasibility, cost, impact and preferred method of automating the NIH Library using computer technology. We expect in the coming year to collaborate further with the NIH Library, to issue an RFP for the principal elements of the automation system, and to develop those elements which are not available commercially.

Voice Output Terminal for the Blind: Using technology originally designed for medical telecommunication projects, a voice output terminal has been implemented for use by a blind computer programmer. A microcomputer combined with a speech synthesizer form the basis of a linkage module between a standard alphanumeric computer terminal and any available host computer. Transparent to the host computer, all data routed to the terminal is intercepted in the microcomputer and is converted to phonetic codes using English rules of pronunciation. Data edit features are offered to alter the speed and translated content of speech output; data review options are available to permit the repetition or spell-back of poorly understood text output. A prototype terminal has been field tested by a blind programmer for over six months and has significantly increased his productivity. The terminal was exhibited at the 1979 annual meeting of the President's Committee on Employment of the Handicapped in Washington, D.C. Present plans call for the hardware development of low-cost portable units (under $3,000 for components) and the software design for additional voice output devices with more general application for the visually impaired.

In Vitro Information System, NCI, DCCP: The National Cancer Institute conducts an in vitro testing program under the Carcinogenesis Bioassay Program. In vitro and submammalian assays provide information as to the genetic potential of chemicals; many chemicals which are mutagenic are also carcinogenic. The development of a battery of in vitro assays to serve as a screening method for selection of candidates for carcinogenic testing in vivo is therefore desirable, since the latter are much more time-consuming and expensive.

In the interest of improving the quality and timeliness of data from the In Vitro Program, CSL was asked to investigate the applicability of source data collection techniques to the acquisition of mutagenesis data. A study was performed in early 1979, leading to the finding that source data collection was both feasible and desirable, and recommending that a contract be let for a pilot program development utilizing programmable, microprocessor-based, intelligent terminals.

LEVEL OF EFFORT AND CAPITAL EXPENDITURE BY MAJOR PROJECT (July 1978 - September 1979)

Project Title	Project Leader	Effort (Man Years)	DCRT Capital Invested*
Computerized Radiotherapy, NCI, RO	Syed	3 1/2	10K
Medical Intensive Care Unit, CC, DCCM	Syed	2 1/2	55K
Cardiac Intensive Care Unit, NHLBI, SU	Syed	2 1/2	0K
Nuclear Medicine, CC	Plexico	1 1/2	45K
Automated ECG Processing, CC & NHLBI, IR CB	Plexico	1/6	0K
Pulmonary Branch, NHLBI	Plexico	1/6	0K
Clinical Pathology, CC	Plexico	3/4	5K
Image Analysis, CSL	Syed	3 1/2	2K
Distributed Data Acquisition & Control System, NIAMDD	Schultz	4 1/2	35K
Scanning Electron Microscope, NIAMDD & NCI	Schultz	1/6	30K
Flow Microfluorometry, Cell Sorter, NCI, I, LP & NIAID, LMI	Schultz	2	14K
Selected Ion Recording System NIMH, LCS	Schultz	1 1/2	10K
Analytical Ultracentrifuge Data System, NHLBI	Schultz	1/6	0K
Microanalysis Facility, DRS, BEIB	Plexico	3/4	4K
Microcomputer Based Controller for Evoked Response Experiments, NIMH, LBEB	Plexico	1/2	1.3K
Spectrophotometer Data Logger, NIDR	Plexico	1/2	8K
Amino Acid Analyzer Data Logger, NCI	Plexico	1/4	9K
Radiation Counter Data Recorder, CSL	Plexico	3/4	27.5K
NIEHS Computer Facility	Plexico	1/6	0K
Bioassay Information System, NCI, DCCP & FDS, NCTR	Plexico	1/2	0K
Laboratory of Immunology, NIAID	Plexico	1/2	0K
Laboratory of Chemical Biology, NIAMD	Plexico	1/2	4K
Potentiometric Titration Controller, NHLBI, IR LC	Plexico	1/4	5K
Computers in Cardiology Conference	Schultz	1/6	6K
NIH Library Automation, DRS	Syed	1	0K
Voice Output Terminal (Blind)	Plexico	2	1K
CSL Development System	Plexico	1/6	35K
In Vitro Information System, NCI, DCCP	Plexico	1/6	0K

*CSL Budget exceeds this total, due to purchases of support items which are not charged to individual projects.

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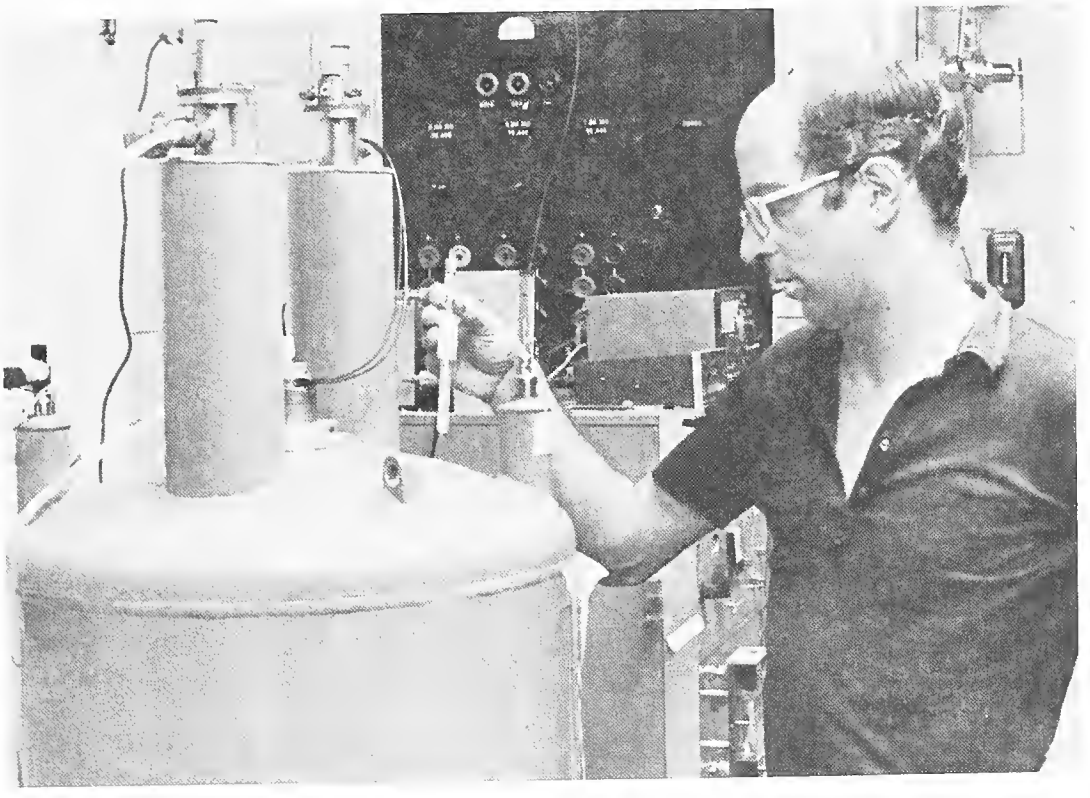
Ostrow, H., Allen, S., Bacharach, S., Green, M., and Borer, J.: A Gated Probe System for Real-time Creation of Pressure Volume Loops. Journal of Nuclear Medicine, Vol. 20, June 1979, p. 610.

Plexico, P., and Kempner, K.: Microcomputers in Medicine. Infotech International, Ltd., Maiden, Berkshire, England (in press).

Since FY75, CSL has provided engineering, system integration, and software support to meet the data acquisition, data display, and analysis needs of NIH investigators using Flow Microfluorometers. Evaluating some enhancements are Donald Jansen, John Powell, and Arthur Schultz.

PHYSICAL SCIENCES LABORATORY

George H. Weiss
Chief



Dr. James Ferretti works on developing new methods of nuclear magnetic resonance spectroscopy (NMR) and on applying NMR to the study of small proteins. In the past year, experimental studies have been conducted on the interaction of iron with bleomycin, an important anticancer compound.

I. SUMMARY

Function

The Physical Sciences Laboratory has three principal functions:

- to carry out research in the physical sciences in order to understand biological phenomena in terms of physics and chemistry
- to develop the theory and practical instrumentation for biomedical experiments, and in particular to relate these to the capabilities of modern computer technology
- to provide consulting services to other scientists at NIH in physics theoretical chemistry, and several fields in applied mathematics.

The staff of the Physical Sciences Laboratory consists of six professionals who work in the areas of general biophysics, nuclear magnetic resonance, applications of light scattering techniques in biomedical experiments, the physical chemistry of polyelectrolytes and problems in applied mathematics.

Scope of Work

The Physical Sciences Laboratory has a combined program of research projects internal to the laboratory and collaborative projects with scientists at NIH and at other institutions. These collaborative projects are done jointly with approximately twenty five other investigators including two major projects with data being generated by off-campus scientists.

Highlights of the Year's Activities

In the past year progress was made in most of the PSL continuing projects, and a start was made in two new areas.

Dr. Stephen Brenner has begun an experimental study of the interaction spectrum with actin. This work is carried out in the laboratory of Dr. E. Korn, NHLBI. So far the work has been devoted to purifying sheep erythrocyte spectrin and rabbit skeletal muscle actin, and studying their interaction. Spectrin is thought to play a dominant role in determining the shape of red blood cells.

A second new project is one on the quantitative analysis of electron-micrographs initiated by a newcomer to the PSL, Dr. Nachum Gershon. Electron micrographs of different systems of biological interest are being furnished by collaborators both on and off the NIH grounds. The systems include virally infected cancer cells and insulin receptors on rat adipocytes.

Dr. Parsegian continued a systematic study of forces between phospholipid bilayer membranes immersed in solution together with experimental collaborators at Brock University, led by Professor Peter Rand. He discovered a new class of forces that appears to dominate the interaction of biological membranes at distances of less than 30 Å. These forces to the work of removing water from cell surfaces. A related part of this project is making mechanical measurements of the deformability of membranes. Preliminary results in this area differ from those that one would expect from studies of phospholipid monolayers. Dr. Gingell of the Middlesex Medical School, who has been collaborating with Dr. Parsegian on studies of forces in biological structures, has shown that cells can be held to surfaces by long-range electromagnetic forces which act at thousands of Angstroms distance.

Dr. Parsegian's project has led to the development of powerful new theoretical and experimental tools that allow one to study physical forces at distances of the order of tens of angstroms. There is considerable potential for studying different biological systems with these tools, such as protein aggregation, interactions within hemoglobin, and gelation. These projects await additional personnel to implement presently available methods.

Dr. Nossal continued to develop theoretical and experimental techniques for using laser systems to measure different parameters in biologically interesting materials. The most recent work in this field has been in the measurement of elastic coefficient in gels. Much of this work has been performed with Dr. R. Gelman, NIDR. Dr. Nossal, together with Dr. J. Gladner, NIAMDD is completing a study of fibrin gels to find a relation between the mechanical strength of blood clots and the interchain crosslinking of the constituent proteins.

Dr. Weiss continued working with Dr. W. F. Caveness, NINCDS, on the analysis of a large data base of medical data on head injured veterans of Vietnam. Several studies of this data have been completed. These include the occurrence of post traumatic epilepsy, the consequences of using different materials for cranioplasties, and the origin and persistence of aphasia. Different injury parameters could be related to the onset of aphasia, but no reliable prediction could be made of the disappearance of aphasia based on what is known about the injury.

Dr. Weiss was appointed to the Board of Editors of the Journal of Statistical Physics

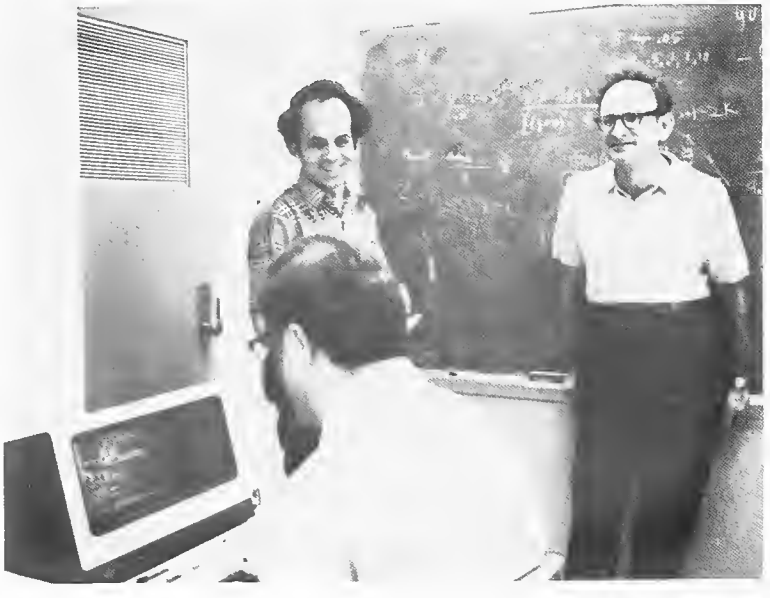
Future Plans

All of the research projects of the laboratory will continue. We see no change in direction or emphasis within the coming year.

The experiments on forces operating in membranes will continue, and there is a possibility that a new series of measurements will be made on forces between proteins.

A study of the physical properties of clathrin baskets will be undertaken by Dr. Nossal. This investigation will help to elucidate the structure of these biologically important molecules as well as the measuring hydrodynamic parameters.

Investigators at the University of Connecticut will undertake experiments on the acceleration of sedimentation equilibrium experiments. The theory for this technique was developed by Dr. Weiss in collaboration with Professor Yphantis at the University of Connecticut.



The Physical Sciences Laboratory has a combined program of research projects internal to the laboratory and collaborative projects with scientists at NIH and at other institutions. Here visiting Israeli scientist Dr. Nahum Gershon (left) and PSL Chief Dr. George Weiss (right) discuss a study with James Kiefer (seated).

Theory of Biochemical Separation Techniques. George H. Weiss, PSL, in collaboration with Professor D. A. Yphaantis, University of Connecticut. This is a joint theoretical and experimental project to develop techniques for interpreting measurements made by such methods as ultracentrifugation and electrophoresis. There was little activity on this project in the last year except for some tests of different methods of inverting sedimentation equilibrium data to measure molecular weight distributions.

Theory and Measurement of Intermolecular Forces. V. Adrian Parsegian, PSL, in collaboration with Professor P. Rand, Brock University and Dr. D. Gingell, University of London. This project consists of laboratory investigations based on theoretical techniques developed by Dr. Parsegian for measuring forces that operate at short distances. In the past year the project participants have discovered and measured a new force in the interaction of phospholipid membranes at distances of 30Å or less. This force has been attributed to the work required to squeeze water molecules out from between the membranes.

Consulting Services. George H. Weiss, PSL. This project includes elements of epidemiology and the development of mathematical techniques applied to specific problems of NIH researchers. A considerable amount of time was spent on several studies of a large data base on head-injured Vietnam veterans related to the occurrence of posttraumatic epilepsy, aphasia, the treatment of severe head injuries, and the use of different cranioplasty materials. A study was completed on interpolation in computerized tomography and a new collaboration was begun on the development of a theory to interpret experiments on DNA fractionation.

Correlation Function Spectroscopy/Laser Light Scattering. Ralph J. Nossal, PSL, in collaboration with Drs. R. Gelman, NIDR, R. Bonner, DRS, and J. Gladner, NIAMDD. This project comprises laboratory investigations and development of theory for interpretation of experiments. In the past year Dr. Nossal developed a theory to enable one to measure elastic coefficients of soft biological gels. These were used in a study of elastic moduli in polyacrylamide gels.

Cell Motility and Chemotaxis. Ralph J. Nossal, PSL, in collaboration with Dr. L. Lipkin, NCI. This project is a combination of laboratory experiments and the development of theoretical models to elucidate factors that influence cell locomotion and chemotaxis. Experiments are currently in progress on the response of neutrophils to different chemical factors produced by stimulated lymphocytes. Algorithms and computer programs have been developed to automate cell tracking experiments.

Theory and Application of Nuclear Magnetic Resonance Spectroscopy. Dr. James A. Ferretti, PSL, in collaboration with Drs. E. Becker, NIAMDD, R. Highet, NHLBI, G. Weiss, PSL and G. Marshall, Washington University.

This project consists of laboratory experiments and concurrent development of theory for the application of NMR to elucidate the structure and function of biologically interesting chemicals. In the past year experimental studies have been conducted on the interaction of iron with bleomycin, an important anticancer compound, and on bradykinin and gramicidin S. Similar investigations are continuing. Further analyses of the techniques of NMR are being carried out with a view to measuring spin-lattice relaxation times as accurately as possible in a fixed time.

Interactions of Erythrocyte Spectrin with Actin. Stephen L. Brenner, PSL, in collaboration with Dr. E. Korn, NHLBI. This is a laboratory investigation of the properties of a molecule believed to be important in determining the shape of red blood cells. Different forms of spectrin exist. This year was devoted to finding the elastic properties of these variant forms.

Quantitative Analysis of Electronmicrographs and Membrane Cellular Biophysics. Nachum Gershon, PSL, in collaboration with Dr. B. Bowers, NHLBI, L. Jarett, and R. Smith, Washington University. This project is a methological one using data gathered in different laboratories to determine configurational properties of proteins on cell surfaces. In the past year several studies were initiated, computer programs were written, and algorithms developed. An example of a project now under way is a joint study to determine whether the surface of phagocytosing cells has a different protein content than does its interior.

Studies in Mathematics and Statistics. George H. Weiss, PSL, James E. Kiefer, PSL, in collaboration with R. J. Rubin, National Bureau of Standards and I. G. Darvey, Sydney University. This project includes several unrelated investigations in numerical analysis and applications of mathematical problems in chemistry. A study was completed on determining the best technique for accelerating the convergence of slowly convergent Fourier series. Further investigations were made of the properties of random walks relevant to the description of polymer configurations. Some work was done on optimal design of enzyme kinetic experiments.

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Weiss, G. H.: Transport equations with quadratic nonlinearities. Sep. Sci. 14: 243-246, 1979.

Weiss, G. H.: A note on occupation times of random walks. J. Stat. Phys. (to appear).

Weiss, G. H., Rubin, R. J.: Internal coordinate of span-constrained random walks. J. Stat. Phys. (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00014-12 PSL

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Theory of Biochemical Separation Techniques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. H. Weiss, Chief, Physical Sciences Laboratory
Other: D. A. Yphantis, Professor of Biology, University of Connecticut

COOPERATING UNITS (if any)
None

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, MD

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☑ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project explores the use of different mathematical methods to aid the interpretation of Biochemical separation experiments by such techniques as ultracentrifugation and electrophoresis. Some exploratory work was done on the use of regularization techniques for deriving molecular weight information from sedimentation equilibrium experiments on inhomogeneous proteins.

Only a small effort was expended on this project in the past year. Our efforts to apply regularization methods to the derivation of the moments of molecular weight distributions seemed to indicate that only the lowest moment can be obtained with any degree of confidence.

Keyword Descriptors: Ultracentrifugation, equilibrium sedimentation, regularization techniques.

Publications:

Weiss, G. H.: Transport equations with quadratic nonlinearities. Sep. Sci. 14, 243-246, 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00026-04 PSL

PERIOD COVERED

October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Theory and Measurement of Intermolecular Forces

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: V. A. Parsegian, PSL,DCRT
G. H. Weiss, PSL,DCRT
D. O. Tinker, University of Toronto
J. E. Kiefer, PSL,DCRT

Others: R. P. Rand, Brock University
L. Lis, Brock University
S. Cowley, Brock University
M. McAlister, Brock University
N. Fuller, Brock University
D. Gingell, Middlesex Medical School

COOPERATING UNITS (if any)

None

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, MD.

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.3	2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project aims to understand the role of intermolecular forces in biological phenomena. A major topic has been the measurement of forces between phospholipid bilayer membranes immersed in water. We are also measuring intermolecular forces between lipids in the same membrane.

We have discovered a new class of "hydration" forces that appear to dominate the interaction of biological membranes at distances less than 30Å. These forces are independent of electrical charge on the membrane surface and drop off exponentially with a decay constant about the dimension of a water molecule. It is these forces, reflecting work of removing water from the cell surface, that seem to control physical contact between membranes.

We have measured the deformability of membranes and succeeded in forcing aggregates of molecules to go through phase transitions while measuring the work of creating the transition.

Theory and Measurement of Intermolecular Forces

With Professor Peter Rand of Brock University we continue to make measurements of forces between phospholipid bilayer membranes. This includes several estimates of the van der Waals force between bodies in water. The results published so far are a series of systematic studies on the physical properties of cell membrane lipids. We hope to extend these then to direct observations of forces between natural cell membranes. We have been able also to measure forces between molecules within the same membrane. This finding has opened up new means to determine the mechanical properties of artificial and natural membranes.

It is clear now that, upon their close approaches, the dominant force between membranes that are stable in water is due to the work of removing water from between their approaching surfaces. This forces dies off exponentially and is independent of electric charge on the membrane surface. In natural systems it poses a final and imposing barrier to contact between different membranes.

We now have mechanical measurements of the deformability of phospholipid bilayer membranes. The results differ markedly from what is expected from the study of phospholipid monolayers and will provide critical information for testing models of membrane stability and structural transition.

In one particular instance we have observed the adsorption of charged particles (ions) to membrane surfaces by measuring the effect of that adsorption on electrical forces between membranes. The force measurement then becomes a measure of the reactivity of ion with surface as it depends on electrical potential of the reacting surfaces, distance between membranes, and the ionic conditions of the bathing medium. Alkaline earth ions bind strongly to all phospholipid membranes with a specificity that depends on ion type as well as packing of the phospholipid molecules.

With Dr. David Gingell of London, England, we have been studying the interactions of red cells with each other and with artificial materials. Guided by the theory of forces as developed in this laboratory, we have devised and performed experiments demonstrating that cells can be held to surfaces by long-range electromagnetic forces, which have now been shown to act at thousands of Angstroms separation. As a result of these studies we now suggest that long-range association is not a useful concept for studying contact between cell surfaces in physiological saline since the predicted minimum is less than the likely distance of protrusion of glycoproteins from the cell surface. The weakness of long-range forces far from cell contact is such as to render them unable to confer mechanical stability at long distances.

Publications

Cowley, S., Fuller, N., Rand, R. P. and Parsegian, V. A.: Measurement of repulsion between charged phospholipid bilayers. Biochemistry 17, 3163-3168, 1978.

Kiefer, J. E., Parsegian, V. A. and Weiss, G. H.: Some convenient bounds and approximations for the many body van der Waals attraction between spheres. J. Coll. Int. Sci. 67, 141-153, 1978.

Brenner, S. L., Parsegian, V. A., and Gingell, D.: The effects of image forces on double-layer interactions. J. Phys. Chem. 82, 1727-1731, 1978.

Lis, L. J., Rand, R. P. and Parsegian, V. A.: Measurement of the adsorption of Ca^{++} and Mg^{++} to phosphatidyl cholines bilayers in Bioelectrochemistry: Ions, Surfaces and Membranes. American Chemical Society, Washington, D. C., Ed. M. Blank, 1979.

Parsegian, V. A., Fuller, N. and Rand R. P.: Measured work of deformation and repulsion of lecithin bilayers. Proc. Nat. Acad. Sci. (USA) (in press).

Parsegian, V. A.: Competitive forces influencing the interaction of biological cells. Proceedings of the Feb. 1979 Workshop on Interfacial Phenomena, University of Washington, Seattle, Ed. J. Berg (in press).

Parsegian, V. A. and Gingell, D.: Determination of the repulsive force sufficient to prevent adhesion of red cells to planar surfaces. Experimental Cell Research (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00022-12 PSL

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Consulting Services

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. H. Weiss, Chief, Physical Sciences Laboratory, PSL,DCRT

COOPERATING UNITS (if any)

W. F. Caveness, M.D., Chief, LEN, NINCDS, R. A. Brooks, Ph.D., SN, NINCDS
I. M. Chaiken, Ph.D., LCB, NIAMDD, K. W. Kohn, Ph.D., LMPH, NCI
B. W. Bunow, Ph.D., LAS, DCRT

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Division of Computer Research & Technology, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.8	0.7	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Members of the PSL provide consulting services to scientists and physicians at NIH in different areas of applied mathemtics and the physical sciences. A large segment of this effort is devoted to a study of the effects of head injury in veterans of Vietnam.. We have continued our study of interpolation error in computerized tomography. We have examined experimental data and suggested further experiments with affinity chromatography to discover the causes of discrepancies from theoretical predictions. We have worked on combinatorial problems that arise from a method of fractionating DNA by alkaline elution.

Consulting Services

The PSL has provided computer services and statistical assistance to Dr. W. Caveness, NINCDS for the analysis of data on 1220 head injured Vietnam veterans. In particular a study of post traumatic epilepsy in these veterans showed that the rate of occurrence of this sequela was approximately the same as that for veterans of world wars 1 and 2, and the Korean war. This occurred in spite of advances in treatment particularly the prophylactic use of anticonvulsants. Furthermore, the pattern of onset agrees with the historical data. A second study of the data related to the use and effectiveness of different cranioplasty materials. We found that the risk of complications was significantly reduced if cranioplasty was delayed for at least a year after the initial operation. Furthermore no significant differences were detected that could be attributed to the different materials used in cranio-plasties. A study of the origin and persistence of aphasia as well as correlation with motor deficits is presently being completed. We have found several factors that can be correlated with the onset of aphasia, but none have so far appeared that can be associated with its disappearance.

A study with R. A. Brooks, NINCDS on discretization and interpolation errors in computerized tomography is nearing completion. We have focussed attention on obtaining an exact reproduction of a reconstructed delta function using Fourier techniques that we developed earlier. Using these techniques we have been able to demonstrate the origin of Moire patterns found in earlier empirical reconstructions.

We have investigated, in some depth, the theory underlying affinity chromatography for Dr. I. M. Chaiken, NIAMDD, to try to explain some discrepancies between his experimental data and the theory. A tentative physical explanation has been found, but it must be examined further experimentally. Recently we have started to work on several combinatorial problems for Dr. K. W. Kohn, NCI, required for the design of experiments of fractionation of DNA strands by alkaline elution.

Together with several members of LAS, DCRT, we have developed a theory of noise in lung scanning. The theory allows one to choose experimental parameters that lead to small values of bias and variance.

Keyword Descriptors: Head injuries, post traumatic epilepsy, cranioplasty, aphasia, interpolation errors, discretization errors, computerized tomography, Moire patterns, affinity Chromatography, fractionation, lung scanning.

Publications

Brooks, R. A., Weiss, G. H., Talbert, A. J.: A new approach to interpolation in computed tomography, J. Comp. Tomog. 22, 577-585, 1978.

Chew, E., Weiss, G. H., Brooks, R. A., DiChiro, G.: Effect of CT noise on detectability of test objects. Am. J. Roentgen. 13, 681-685, 1978.

Gail, M. H., Weiss, G. H., Mantel, M., O'Brein, S. J.: A solution to the generalized birthday problem with application to allozyme screening for cell culture contamination. J. Appl. Prob. (to appear).

Bunow, B., Line, B. R., Morton, M. R., Weiss, G. H.: Regional ventilatory-clearance by xenon scintigraphy: A critical evaluation of two estimation procedures. J. Nucl. Med. (to appear).

Meirowsky, A. M., Caveness, W. F., Rish, B. L., Dillon, J. D., Mohr, J. P., Kistler, J. P., Weiss, G. H.: Definitive care of cerebral missile injuries crossing the midline. Mil. Med. (to appear).

Caveness, W. F., Meirowsky, A. M., Rish, B. L., Mohr, J. P., Kistler, J. P., Dillon, J. D., Weiss, G. H.: The nature of post tranumatic epilepsy. Arch. Neurol. 50, 545-533 (1979).

Rish, B. L., Dillon, J. D., Meirowsky, A. M., Rish, B. L., Mohr, J. P., Kistler, J. P., Weiss, G. H.: Cranioplasty: A review of 1030 cases of penetrating head injuries. Neurol. (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00021-08 PSL

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Correlation Function Spectroscopy/Laser Light Scattering

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. J. Nossal, Ph.D., Research Physicist, PSL,DCRT

COOPERATING UNITS (if any)

J. Gladner, Ph.D., Laboratory of Biophysical Chemistry, NIAMDD
R. Bonner, Ph.D., Biomedical Engineering & Instrumentation Branch, DRS
R. Gelman, Ph.D., Laboratory of Biochemistry, NIDR
H. T. Pretorius, M.D., Clinical Endocrinology Branch, NIAMDD

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, Md

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.8	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Experimental and theoretical studies have been performed to develop laser inelastic light scattering methods for studying biological gels and other materials. The technique is being used to examine the strength of fibrin clots. Studies also are being performed in order to understand how laser Doppler techniques can be used to measure capillary blood flow in tissues. An investigation of the structure of brain-tissue derived clathin "baskets" has been started.

Correlation Function Spectroscopy/Laser Light Scattering

The primary objective of this project is development of laser inelastic light scattering techniques for performing rapid and precise measurements on biological systems and materials. In principle, any process giving rise to refractive index fluctuations can be monitored. The instrument which we have constructed has been used to measure diffusion coefficients of macromolecules, swimming speed distributions of motile microorganisms, elastic moduli of gels and blood flow in capillaries.

During the past year we improved a scheme for measuring elastic coefficients of dilute polymer networks and soft biological gels developed by us in the past year. A new theory was developed to account for internal energy dissipation by the polymer lattice. Several collaborative studies utilizing this new technique were undertaken. Experiments on polyacrylamide gel models were performed, and the manner in which elastic moduli depend upon parameters such as temperature and concentration was determined (with R. Gelman, NIDR). Fibrin gels were studied in order to obtain insight into the relationship between the mechanical strength of blood clots and the nature and extent of interchain crosslinking of protein constituents (with J. Gladner, NIAMDD).

Experiments also have been undertaken to examine how laser Doppler techniques can be used to measure tissue blood flow. Dr. R. Bonner (BEIB) is developing a laser Doppler flowmeter for clinical use, and we have collaborated on experiments utilizing synthetic flow models to determine relationships between measured spectra and such variables as blood density, flow rate, and back-scatter illumination from surrounding tissue. A mathematical theory for data interpretation has been derived.

Keyword Descriptors:

Laser light scattering, macromolecules, diffusion coefficients, correlation functions, gels, blood flow.

Publications:

Gelman, R. A. and Nossal, R.: Laser light scattering from mechanically excited gels. Macromolecules 12, 311-316, 1979.

Nossal, R.: A theory of quasielastic laser light scattering by polymer gels. J. Appl. Phys. 500, 3105-3112, 1979.

Bonner, R. F., Bowen, P., Bowman, R. C. and Nossal, R.: Real-time monitoring of tissue blood flow by laser Doppler velocimetry. Proceedings Electro-Optics/Laser '78 Conference, pp 539-550, Industrial and Scientific Conference Management, Inc. Chicago, Illinois, 1978.

Gelman, R. A., Gladner, J. A. and Nossal, R.: The rigidity of fibrin gels as measured by quasielastic light scattering. Biopolymers (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00017-07 PSL

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Cell Motility and Chemotaxis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. J. Nossal, Research Physicist, PSL,DCRT

COOPERATING UNITS (if any)
L. Lipkin, M.D., Image Processing Unit, DCBD, NCI

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, MD

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been undertaken to study various aspects of cell locomotion and chemotaxis. Analytical expressions to quantitate capillary migration (MIF) assays have been derived. New procedures for measuring macroscopic coefficients of cell migration are being developed, including computer assisted tracking techniques. Studies of the manner in which lymphokines affect the migration of individual leukocytes are in progress.

Cell Motility and Chemotaxis

This study relates to cell locomotion and chemotaxis. Recent emphasis has been on examining certain immunologic aspects of leukocyte migration.

As part of this project, a general mathematical theory for interpreting results of capillary migration assays for cellular immune sensitivity (MIF tests) was derived. However, various basic parameters of leukocyte movement which are necessary for quantitating the assay are not well known. Consequently, collaborative experiments now are being performed with Dr. Lewis Lipkin (DCBD/NCI) which involve studying the response of neutrophils to various chemical factors ("lymphokines") produced by stimulated lymphocytes. Specialized measurement techniques have been devised, an example of which is a scheme where occupation number fluctuations are analyzed to determine mobility coefficients of migrating cells. Also, algorithms and computer programs have been developed to adapt an automated microscope system for cell tracking experiments. This instrument will be used to examine the behavior of neutrophils when responding to chemoattractants. Prototype measurements have been performed which now are being analyzed.

Publication

None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00025-04 PSL

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Theory and Application of Nuclear Magnetic Resonance Spectroscopy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: James A.Ferretti, Ph.D., Research Chemist, PSL,DCRT

Other: E. D. Becker, Chief, Laboratory of Chemical Physics, LCP,NIAMDD
G. R. Marshall, Professor of Physiology, Department of Physiology and Biophysics, Washington University School of Medicine, St. Louis, Mo.
R. J. Highet, Laboratory of Chemistry, NHLBI
G. H. Weiss, Chief, Physical Sciences Laboratory, PSL,DCRT

COOPERATING UNITS (if any)

Laboratory of Chemical Physics, NIAMDD

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, MD

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to develop new methods in nuclear magnetic resonance spectroscopy and also to apply NMR to the study of small proteins. In particular, development of the correlation method of obtaining NMR spectra is of special interest. An experimental and theoretical study of interference effects in correlation spectroscopy has been undertaken. Saturation effects in correlation NMR are currently being studied. Investigations of the solution conformation of derivatives of angiotensin, bradykinin and bleomycin are in progress. In these systems we have demonstrated the importance of the contribution of internal motion to the relaxation behavior.

The magnetic field strength and temperature dependences of the spin-lattice relaxation times, T_1, spin-spin relaxation times, T_2, and nuclear Overhauser enhancement (NOE) factors in small peptides are continuing to be studied. Studies on Angiotension-II and a heptapeptide analog at pH 4.3 have recently been completed and similar studies at pH 8.3 are ongoing. In the course of this pilot investigation on angiotensin-II, it was necessary to develop a mathematical model for analyzing the field strength dependence of the T_1 values in terms of the overall and internal reorientational correlation times. Such knowledge is useful in understanding interactions at the receptor site. Use of the model in this fashion yields T_2 and NOE values which are in good agreement with those which are experimentally observed. These results have permitted us to establish the nature of the molecular associations in solution, estimate the size and shape of the various peptides and also to quantitate paramagnetic ion-peptide distances in the complexes. Similar studies have been carried out also on bleomycin, bradykinin, and gramicidin S. From the temperature and field dependences of the T_1 and NOE values, it has been possible to estimate the relative free energies of activation for both overall and internal motions.

We have completed a study on the interaction of Fe (II) on bleomycin. Bleomycin is a glycopeptide whose iron complex has been shown to be effective against a variety of human neoplasms. The formation of this complex is required for efficient, oxygen-dependent degradation of DNA by bleomycin. The first aspect of this study was to characterize the spin state of the iron and to demonstrate that the complex is paramagnetic. For this purpose we carried out both optical and magnetic resonance measurements to show that the ion in the complex at pH 5-6 is predominantly in the high spin state. With these results and on the basis of field dependent relaxation studies on the carbon atoms of bleomycin and the complex at various molar ratios of iron, we determined the metal-carbon distances for various atoms in the glycopeptide. These results enabled us to propose a mechanism of action of the iron complex on DNA which involves intercalation of the bithiazole rings and where the oxydation of the iron generates free radicals of oxygen which induce rupture and strand scissoring of the DNA.

We have initiated a study on a novel form of vitamin B_{12} (cobalamin). This new isomeric form of vitamin B_{12}, which is achieved by substituting the benzyimidazole base by a less bulky group like OH^- or CN^-, is present as an impurity in all commercially available cobalamins. Preliminary studies suggest that it is at least as active biologically as the major constituent of vitamin B_{12}. Spectra on the new form of cobalamin have been obtained and analyzed and relaxation studies as well as other spectroscopic studies are under way to characterize the structure and conformation of the molecule.

The study of NMR correlation spectroscopy is continuing. We have completed both the experimental and theoretical aspects of the study of the effects of driving the nuclear spin system into its non linear response region. We demonstrate the usefulness of the correlation technique for effective flip angles which approach 90^0. We have also investigated the consequences of the causality principle on the relations between absorption and dispersion mode signals obtained in correlation experiments with particular emphasis on the distribution of information between the two signals.

We are proceeding to analyze additional aspects of NMR spin-lattice relaxation time, T_1, studies determined by various methods. In one previous work we showed that for the problem where T_1 and the equilibrium value of the magnetization are the only unknowns, the fast inversion-recovery technique is often the method of choice. Recently we have considered two new techniques which also incorporate a rapid recycling of pulse sequences. The first method is a variable flip angle perturbation technique. The major advantage to this method is that the data may be plotted on a linear scale with uniform variance. A second method, which is a variant on the fast inversion-recovery methods, gives precisions in T_1 which are approximately as good as those obtained by the normal fast inversion-recovery method. In addition, this method offers some additional advantages in the elimination of effects due to systematic errors in the effective flip angle parameters.

Publications:

Ferretti, J. A. and Marshall, G. R.: Carbon-13 properties of Angiotensin-II. Biophysical J. 21, 79a, 1978.

Benovic, J. L., Ferretti, J. A., and Gupta, R. A.: Carbon-13 NMR and metal binding properties of Bleomycin. Biophysical J. 21, 199a, 1978.

Ferretti, J. A., Marshall, G. R., and Gupta, R. K.: Carbon-13 relaxation parameters of small peptides, "Proceedings of the 20th Collogque AMPERE, Tallinn (1978)," p. XXX, North-Holland, Amsterdam.

Weiss, G. H., Gupta, R. K., Ferretti, J. A. and Becker, E. D.: The choice of optimal parameters for measurement of spin lattice relaxation times. I. Mathematical formulation. J. Magn. Resonance (in press).

Becker, E. D., Ferretti, J. A., Gupta, R. K. and Weiss, G. H.: The choice of optimal parameters for measurement of spin lattice relaxation times. II. Comparison of saturation-recovery, inversion-recovery, and fast inversion-recovery experiments. J. Magn. Resonance (in press).

Ferretti, J. A. and Marshall, G. R.: Field dependent carbon-13 relaxation studies on peptides. I. Aggregation of Angiotension-II, Biophysical J. (in press).

Gupta, R. K., Becker, E. D., Ferretti, J. A. and Weiss, G. H.: A variable perturbation method for nuclear spin-lattice relaxation measurements. J. Magn. Resonance (in press).

Gupta, R. K., Ferretti, J. A., and Caspary, W. J.: Carbon-13 NMR studies of the structure of the iron-Bleomycin complex. Biophysical J. 25, 236a, 1979.

Becker, E. D., Ferretti, J. A., and Gambhir, P. N.: Selection of optimum parameters for pulse Fourier transform NMR. Analytical Chemistry (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT 00040-01 PSL

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Interactions of Erythrocyte Spectrin with Actin

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: Stephen Brenner, Research Chemist, PSL,DCRT

COOPERATING UNITS (if any)
E. D. Korn, Lab. Cell Biology, NHLBI

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH,

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Sheep erythrocyte spectrin and rabbit skeletal muscle actin have been purified and their interactions studied by viscometry and ultracentrifugation. It has been found that the tetrameric form of spectrin crosslinks F-actin filaments to form a gel and that spectrin dimer binds to, but does not crosslink, F-actin. Neither phosphorylation of the spectrin, nor dephosphorylation, was found to affects its interaction with actin. A high molecular weight oligomeric complex of spectrin, actin, and several minor proteins, has been isolated from sheep erythrocyte ghosts. We have found that this complex can induce the polymerization of G-actin. Studies on the mechanism of action of this complex are in progress.

Interactions of Erythrocyte Spectrin and Actin

Spectrin and actin are major components of the cytoskeletal network that is believed to be a determinant of erythrocyte shape and deformability. The primary objective of this project is to determine how spectrin and actin interact to form this cytoskeleton and to examine possible control mechanisms for regulating erthrocyte shape via modulation of spectrin/actin interaction.

Spectrin is purified by gel filtration chromatography of low ionic strength extracts of sheep erythrocyte ghosts. This yields a herero-dimer of a 240,000 and 220,000 dalton polypeptides. The dimer is in simple equilibrium with a tetramer, although inter-conversion is between dimer and tetramer is very slow at low temperatures due to an unusually high activation energy. Equilibrium mixtures of dimer and tetramer are formed at 30-37^{o} and the species separated by gel filtration and stored on ice. We have studied the interaction of spectrin dimer and tetramer with both G-actin and F-actin.

Contrary to published reports we find that highly purified spectrin does not induce the G F polymerization of actin although we have isolated an oligomeric spectrin/actin couple from sheep erythrocyte ghosts which does induce actin polymerization. We find that when small amounts of spectrin tetramer is added to F-actin a highly viscous gel is formed indicating of crosslinking of the actin filaments. Spectrin dimer is totally ineffective as a crosslinker, although ultra-centrifugation studies with radiolabelled (^{32}P) dimer show that it does bind to F-actin. This data suggests that each spectrin dimer possesses a single F-actin binding site with the tetramer, therefore, having two F-actin binding sites. Since the tetramer is believed to be the *in vivo* form, we suggest that the cytoskeleton may be composed of a lattice work of actin filaments crosslinked by spectrin tetramer.

Spectrin is a phosphoprotein and it has been suggested that a kinase/phosphatase couple might control the interaction of spectrin with actin. We have investigated this possibility in detail, both by phosphoylating spectrin with a cAMP-independent kinase isolated from sheep erythrocyte ghosts (1 mole phosphate incorporated/mole spectrin) and by dephosphorylating spectrin labelled *in situ* by incubating red cells with ^{32}P-labelled inorganic phosphate (83% of protein-bound ^{32}P released by alkaline phosphatase treatment). We find the interaction of spectrin tetramer and dimer with F-actin is independent of the state of phosphoylation of the spectrin.

Work in progress includes quantitation of the spectrin/actin binding constants and stoichiometry and studies of the mode of action of the oligomeric complex which induces actin polymerization.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00024-04 PSL

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)
Studies in Mathematics and Statistics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: George H. Weiss, Chief, Phys. Sci. Lab., PSL,DCRT
Other R. J. Rubin, Senior Scientist, NBS
I. G. Darvey, Visiting Scientist, PSL, DCRT
J. E. Kiefer, Research Mathematician, PSL,DCRT
D. E. Blumenfeld, Lecturer, University College, London

COOPERATING UNITS (if any)
None

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.6	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Several unrelated investigations are included in this project. We have completed some work on a comparison of weighting schemes for deriving parameters from kinetic experiments on systems that obey Michaelis-Menten kinetics. We have nearly completed a study of span-constrained random walks that serves as models for the configurations of polymer chains. A third study was in the area of acceleration procedures for speeding the convergence of Fourier series.

Studies in Mathematics and Statistics

We have completed a study of different forms of weighting used in the interpretation of data collected from kinetic experiments on systems that follow Michaelis-Menten kinetics. We have compared approximately twenty different forms of weighting and showed, by simulation techniques, that there is little difference between weighting schemes when the linearized form of the Michaelis-Menten equations is used, but there are definitely preferred weights when data is analyzed directly.

Together with Dr. R. J. Rubin we have developed the theory of span constrained random walks in an attempt to explain simulation experiments on the configurations of polymer chains. The observation has been that two qualitatively different configurations can occur depending on the size of chain. This observation has now been confirmed by our theoretical calculations.

Our work on the acceleration of Fourier series was motivated by earlier applications of numerical methods for inverting Laplace transforms. There we found that the resulting series showed incredibly slow convergence in many instances. We have found extremely good results using an iterated summation by parts. This technique is as good or better than the currently recommended algorithm for accelerating the convergence of Fourier series.

Keyword Descriptors: Least square weights, Michaelis-Menten reactions, polymer chains, random walks, acceleration of convergence, Fourier series, Laplace transforms.

Publications:

Blumenfeld, D. E., Weiss, G. H.: Curve fitting the probability distribution of acoustic noise form freely flowing traffic. Transp. Res. 12, 111-114, 1978.

Blumenfeld, D. E., Weiss, G. H.: Statistics of delay for a population of drivers with step and distributed gap acceptance functions. Transp. Res. 12, 423-429, 1978.

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Bunow, B. Weiss, G. H.: How chaotic is chaos? Chaotic and other "noisy" dynamics in the frequency domain. Math. Biosc. (to appear).

Dishon, M., Weiss, G. H.: Numerical inversion of Mellin and two-sided Laplace transforms. J. Comp. Phys. 28, 129-132, 1978.

Weiss, G. H. A note on occupation times of random walks, J. Stat. Phys. (to appear).

Weiss, G. H., Rubin, R. J.: Internal configurations of span-constrained random walks. J. Stat. Phys. (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00041-01 PSL

PERIOD COVERED
October 1, 1978 to September 30, 1979

TITLE OF PROJECT (80 characters or less)

Quantitative Analysis of Electronmicrographs and Membrane Cellular Biophysics.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: N. Gershon, Ph.D., Visiting Scientist, PSL,DCRT

Other: L. Jarett, Head, Division of Laboratory Medicine Washington University School of Medicine, St. Louis, MO.

R. Smith, Washington University School of Medicine, St. Louis, MO.

B. Bowers, LB, NHLBI

COOPERATING UNITS (if any)

None

LAB/BRANCH
Physical Sciences Laboratory, DCRT

SECTION

INSTITUTE AND LOCATION
Division of Computer Research & Technology, Bethesda, MD

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Methods of quantitating electron micrographs of protein particles on membranes were developed and applied to the analysis of cancer cells infected by viruses, and to insulin receptors in rat adipocytes. Mobility of cell membrane proteins and their interaction with cytoskeletal elements.

In the past few months we have been mainly concentrated working on the following subjects.

(1) Quantitative methods in electron microscopy. We have developed quantitative methods to analyze electronmicrographs of biological systems. The methods includes digitization of micrographs and computational analysis of their contents (e.g. protein particles on membranes). The systems that have been analyzed so far are the following:

(a) For a virally infected cancerous cells we have found that the viral glocyproteins are distributed in a nonrandom fashion on the cell surface even at non-permissive temperatures where the viral buds cannot be formed. This work was done in collaboration with Dr. A. Demsey.

(b) In rat adipocytes we have examined insulin receptors. We are interested in elucidating the mechanism of insulin action on cells. Using ferritin-insulin it is possible to visualize insulin binding sites. Electronmicroscopy shows that the insulin binding sites, which are mostly located on the glycocalyx, are aggregated into discrete groups. Cytochalasin B, a pharmacological agent and a potent glucose transport inhibitor is found to disrupt groups of insulin binding sites while not interferring with its other biological activities. The quantitative analysis shows that binding sites separated by distances of the order of 300Å -400Å are likely to be separated by cytochalasin B. This finding suggests that besides the functional linkage of the insulin and glucose transport system, the latter machinery requires a number of groups of molecules to be aggregated where the distance between consecutive insulin binding sites is of the order of 300Å-400Å. An additional detailed analysis shows that the distances between individual binding sites in pairs are about the same in adipocytes with or without the treatment of cytochalasin B. This work is done in collaboration with Dr. L. Jarett and Dr. R. Smith.

(c) Studies of membranes of phagocytosing cells has been initiated. The analysis will show if the internal regions of the membrane have a different intramembraneous particle content from the cell surface, or they are in a different aggregation state. The study of phagcotosis has its valuable impact on the understanding of cell function and structure especially in circulating cells of the immune system. This work is done in collaboration with Dr. B. Bowers.

(2) Mobility of membrane proteins and their interaction with cytoplasmic components. Membrane proteins can interact with various components inside the cell, e.g. cytoskeletal elements. We have looked for possible physical mechanisms which would account for the attachment of membrane proteins to cytoskeletal filaments e.g. by entanglement or by polymerization of cytoskeletal elements around aggregated membrane proteins. These studies might shed light on how signals are transferred through membranes to cell interiors.

Keyword Descriptors: Electron microscopy, digitization of micrographs, cell surfaces, rat adipocytes, insulin binding sites, cytochalasin B, phagocytosis, membrane proteins, cytoskeleton.

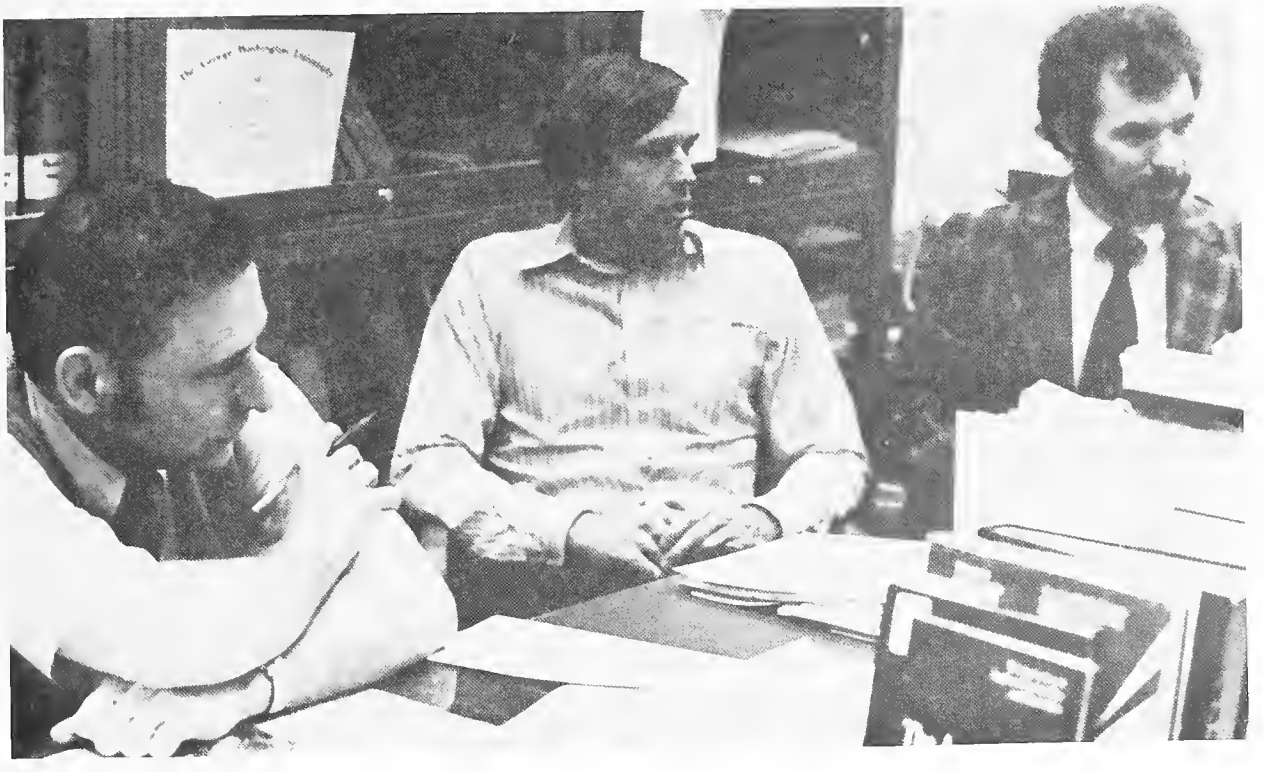
Publications:

N. Gershon, On the effect of crosslinking on the attachment of membrane proteins to the cytoskeleton. Cell Surface Events in Cellular Regulation, Elsevier-North Holland, p. 163 (1979).

N. Gershon, A. Demsey, C. Stackpole, Analysis of local order in the spatial distribution of cell surface molecular assemblies. Exp. Cell Res., (to appear).

LABORATORY OF STATISTICAL AND MATHEMATICAL METHODOLOGY

James E. Mosimann
Chief



LSM staff interact with all NIH institutes and with staff in other Federal agencies outside HEW. In a consultation session (l. to r.), LSM Chief Dr. James Mosimann and Statistical Software Section Head Ray Danner sit with Dr. William Blackwelder of NIAMDD.

I. SUMMARY

Function

The Laboratory of Statistical and Mathematical Methodology (LSM) combines research in mathematical statistics, mathematics, computer and information science, with collaboration and service in these areas to NIH researchers and administrators. The laboratory has 17 full-time positions distributed among four sections:

- The Statistical Software Section (SSS) provides consultation to and collaboration with NIH researchers and administrators in all computational aspects of biomedical data analysis, including selection and support of large program packages. Three specialists in scientific programming are led by a computer systems analyst whose specialty is statistics.

- The Biomathematics and Computer Science Section (BCS), directed by a mathematician, performs independent research and provides consultation and collaboration in the specialties of its eight mathematicians, computer scientists and programming aides.

- The Statistical Methodology Section (SMS) works closely with the Statistical Software Section. Four individuals who work under the direction of a mathematical statistician provide biostatistical consultation and do independent research.

- The Medical Information Science Section (MIS) investigates and develops methods for application of information and computer science to medical language data processing. Five individuals work under the direction of a computer systems analyst who specializes in computational linguistics.

Scope of Work

LSM staff interact with all NIH institutes and with staff in other federal agencies outside HEW. Fiscal year 79 was LSM's fifth year as a separate entity within DCRT. The volume of its computational and consultation services continued to expand while its research activities were maintained at about the same level as the preceding year.

Highlights of the Year's Activities

Computation. A major part of LSM activity is the offering of statistical and mathematical program packages to the NIH user community. LSM accepts responsibility for evaluation of new program packages and their suitability for NIH. When LSM does offer a package to the NIH community, LSM makes three basic commitments:

- The maintenance of the package, with adequate documentation, through NIH computer system changes, package updates and corrections.
- The rapid response to queries concerning user access to a package program including job control language and program parameters.
- The assistance in interpretation of results.

During this year, as in the past year, following program packages and programs were maintained by SSS of LSM.

BMD, BMDP, Biomedical Computer Programs, UCLA SPSS, Statistical Package for the Social Sciences, SPSS, Inc. SAS, Statistical Analysis System, SAS Institute, Inc. PSTAT, Princeton Statistical Package, Princeton University IMSL, International Mathematical and Statistical Libraries, IMSL
Inc. MSTAT1, Collection of Mathematical and and Statistical Programs,
DCRT.

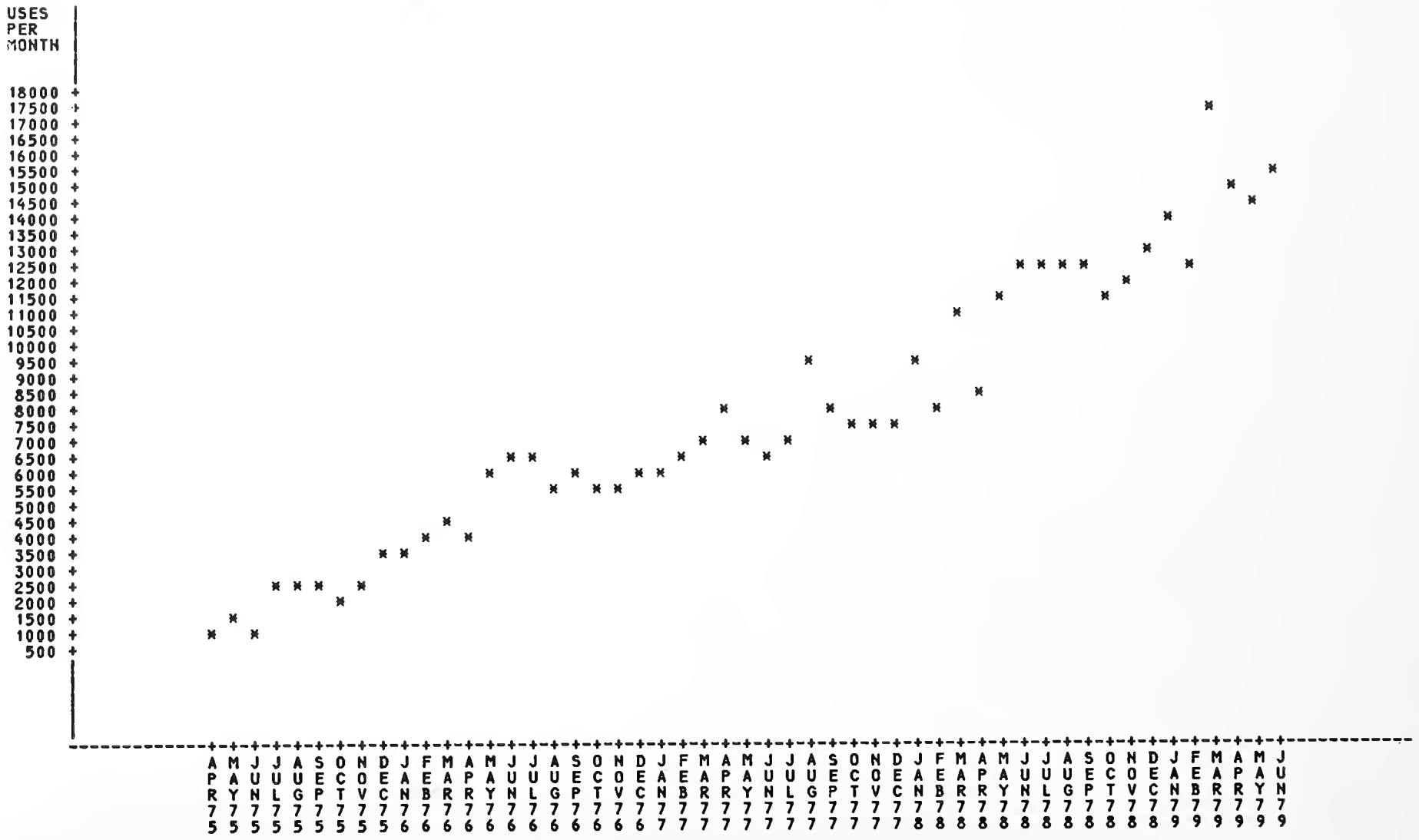
SSS added one additional package, SCSS, during fiscal 79 year. SCSS is an interactive version of SPSS.

The effort expended in the commitment to maintain these packages is considerable. During this year every package went through at least one major update. The effort expended in response to queries concerning package access is also considerable and requires continuous availability. During the year over 4,000 calls were responded to by SSS staff alone. Two courses were taught on each of the SPSS, SAS, and BMDP packages.

The use of program packages continues to show considerable increase. Statistical package use over the past five years is illustrated in Figure 1. The average accesses per month of all the statistical packages rose from almost 9000 during fiscal 78 to over 12000 in fiscal 79. For the third year in a row SAS experienced the largest increase of any of the packages. SAS averages almost 7000 accesses per month, up from 4000 per month in fiscal 78. The

Figure 1

Uses per month of statistical packages supported by LSM (1)



(1) Packages supported by the Statistical Software Section only. Does not include packages supported by the Biomathematics and Computer Science Section.

average number of accesses per month for SPSS increased from 3900 to 4900, an increase of over 55%. The average combined accesses of the BMDP and BMD packages rose slightly from 750 accesses per month in fiscal 78 to around 850 this year. As an example of a package used for specialized purposes, PSTAT averaged 35 accesses per month, up from 20 average accesses per month in fiscal 78. The main programs in MSTAT1 averaged 180 accesses per month, which is slightly above the usage in fiscal 78. The subroutine usage of MSTAT1, which can only be estimated, is much higher than the main program usage. Accesses to the IMSL package cannot be counted, but it is estimated that usage increased during fiscal 79.

In addition to the statistical packages discussed above, the Biomathematics and Computer Science Section maintains the PDP-10 interpretive program MLAB for biomathematical modeling at NIH. This package was designed and implemented by BCS staff, and has been sent to many computer installations here and abroad. Statistics taken at NIH for nine working days during May showed an average of 31 distinct MLAB users each day, with 96 distinct users over the period. During fiscal 79, the documentation for MLAB was expanded. An earlier edition of the MLAB Reference Manual was updated and replaced by two new documents, a concise Reference Manual and an Applications Manual. An extensive Beginner's Guide was completed and will be distributed as soon as the printed copies are received. A Primer was obtained from EPA and distributed to NIH users with changes appropriate to MLAB usage at NIH. BCS research results were incorporated into new MLAB features, including an improved search method for curve-fitting, an operator for interpolation on surfaces in 3-dimensional space, and improvements in hidden-line 3-dimensional graphics techniques.

BCS continues support of C-LAB, a computer package for pattern recognition and cluster analysis developed by a BCS staff member. New documentation for C-LAB was distributed at the beginning of the fiscal year. Minor improvements and corrections were incorporated into C-LAB, and compatability with MLAB was maintained.

BCS staff members taught courses in curve-fitting methods in Mlab in the Fall and Spring, and clustering methods in Clab (Fall). The new manuals cited above facilitated the presentation of the course material.

BCS assumed responsibility for the Unified Generator Package, a software package for generating S/370 assembly language programs for data base management, during the fiscal year. This package was formerly supported by the Data Management Branch, DCRT, and was transferred to BCS support because the program designer joined the BCS staff. A course was taught on the Unified Generator Package during the Fall session, and a paper was given at the Washington ACM Meeting of 12/78, describing the package. The package was maintained and improved during the fiscal year.

A new version of the REDUCE package for symbolic manipulation of algebraic formulas was received from the University of Utah, and it is currently being tested. A software package called PROLOG for symbolic and logical data processing was obtained from the University of Edinburgh. It serves as a computational tool for BCS research, and is currently being evaluated for possible support by the section.

BCS discontinued support of the program package MODELAIDE during the fiscal year, when the BCS staff member who designed the package transferred to the Laboratory of Applied Studies.

Consultation. The diverse nature of LSM consulting is indicated by the projects and activities listed in Part II.

The pattern of LSM consultation activity shifted slightly to more computer-oriented consultation in fiscal 79. Estimated percentages during fiscal 78 and 79 are given below for comparison:

	1978	1979
• Mathematical, statistical and computer computer science advice with limited computer use	10%	5%
• Mathematical or statistical advice with considerable computer use	50%	55%
• Computational advice alone	40%	40%

The continued availability and use of general-purpose statistical and mathematical packages like SAS and MLAB has maintained the large component of computer use in these figures.

As in previous years there was considerable variation in the amount of time required for an LSM consultation. Some very brief consultations are successful, and are brief precisely because there is a known answer to the question posed. Other consultations involve extensive time and statistical/mathematical/ computer science research as well. For example, for the past three years LSM has collaborated with Dr. R. Webber of the Clinical Investigations Branch, NIDR, on the uses of symmetric axis geometry in describing biological shape. One finished study has discussed new shape invariants in the development of the human mandible. The collaboration has involved not only new research in symmetric axis geometry by an LSM staff member, who orginated the concept, but the preparation of innovative computer programs, by LSM and CIB staff. These programs permit interactive examination of shape descriptions, and the generation of shapes from descriptions.

Many consultations which involve considerable LSM effort do not involve new research in computer science. For example, the Unified Generator Package, supported by LSM, was used extensively for a project of Dr. H. Guttman, OD, OPPE, NHLBI. Her data on researchers

associated with NIH grants were collected for use in program management. The Unified Generator Package was used to create the software for maintenance of the data base and for the retrieval of information from it. The author of the Unified Generator Package, an LSM staff member, provided assistance in its use, as well as in the use of the updating, reformatting and reporting systems which were generated.

An example of a long-term effort involving statistical analysis is LSM's study of complications of dialysis in collaboration with Dr's. G. Hirschmann, R. Wineman, and M. Wolfson, all with or formerly with the Artificial Kidney-Chronic Uremia Program of NIAMDD.

A number of statistical consultations involve intensive effort over a period of several weeks. One example would be a study of factors related to case of adopted infants by Dr. R. Klein, Social and Behavioral Sciences Branch, NICHHD. LSM provided the analysis which used the general linear model. A careful study of the hypotheses being tested and their substantive meaning was done.

Research. BCS research included projects in computer science, biomathematics and general mathematical methods. A computer science project for developing heuristic tools for symbolic and logical data processing included applications to computational linguistics and computer generation of symbolic, closed-form solutions to differential equations by applying Laplace transform methods. Research in clustering methods continued, including adaptation and improvement of current methods for generation of minimal spanning trees, and optimal selection of variables for linear regression using branch and bound methods. Study of computer storage and retrieval methods is continuing.

Research in the "symmetric axis" method of shape description was continued, with most effort directed towards extension of the mathematics: (1) to 3-D objects for application to data from a variety of 3-D scanners, and (2) to the direct extraction of descriptions from gray scale pictures, such as X-rays. The BCS investigator in these studies recently presented the results at an NSF workshop in Philadelphia on three dimensional representation of objects.

Research in general mathematical methods continued in the areas of curve-fitting by the sum of absolute difference (L-one) and maximum of absolute difference (L-infinity) criteria, and in methods for analyzing inclusion relations between vector spaces.

In SMS research on multivariate analysis and simultaneous statistical inference was performed. Study on size and shape methods continued, with emphasis on the mathematical transformations connecting the commonly occurring size and shape variables. Applications are to

biological data in the form of ratios or proportions. Research also was initiated in the general linear model for the analysis of unbalanced data. Such data are of common occurrence at NIH. In the area of simultaneous inference, a procedure for multiple ratio estimation was extended to the many sample, unequal covariance, case.

In MIS, their system for the storage and retrieval of pathology information was applied to pathology reports. These natural language reports were encoded automatically by computer into SNOP (The Systematized Nomenclature of Pathology) as well as into ICDO (The International Classification of Diseases for Oncology). Research was continued on the construction of semantically structured dictionaries for pathology. Studies were also continued on rules for automated morphosemantic segmentation of medical compound words derived from Greek and Latin, and for paraphrasing them in English and French medical languages. Work continued on the construction of medical microglossaries for use in small computers.

Future Plans

No major shift in laboratory service or research is anticipated in the coming year. Current levels of support of statistical and mathematical program packages, and consultation and user assistance will be maintained. Research projects will be continuations of those already initiated and reported here.

II. LSM PROJECTS AND ACTIVITIES

Major LSM consulting activities of the year included:

- Clinical research, patient care, epidemiology

Hemodynamic and plasma catecholamine responsis to hyperthermic cancer therapy in humans. Young Kim, AS, CC. Cancer patients treated by induction of hyperthermia under thiopental and fentanyl anesthesia, respond with attenuated hemodynamic changes compared with those reported in normal volunteers. Measured plasma catecholamine at hyperthermic condition showed evidence that sympathetic nerve response to hyperthermia. Statistical procedures used include multiple regression analysis, ANOVA, and descriptive statistics.

Predicting the Onset of Huntington's Chorea. C. Cox, NINCDS, CNB. Neuropsychological measurements, biochemical data, and scan data was collected on 85 subjects including normals, persons at risk, and patients with H. C.. (A person whose parent succumbed to H. C. is thought to have a 50% chance of contracting the disease). Advice and help was given with data management and the use of discriminant analysis and repeated measures ANOVA programs. The discriminant analyses indicated that a certain subgroup on some of the tests.

Triglyceride and HDL Cholesterol. E. J. Schaefer, IR MD, NHLBI. This year the Statistical Analysis System was heavily used as we looked at the effects of several diet types on lipoproteins. A major diet effect was observed when diets such as low fat, high carbohydrate or high polyunsaturated fat were constrasted with ad lib diets in normals and high blood fat subjects. Further work was done in investigating sex and age effects on lipoproteins in normal and dyslipoproteinemic subjects. Results support the earlier conclusion of major sex differences.

Management of epidemiology data. T. Mason, EEB, NCI, and N. Shusterman, ORI. ORI is a consulting firm with an NCI contract to manage a number of epidemiology data bases, involving diverse areas such as breast cancer detection or carcinogens in water supplies. ORI uses the Unified Generator Package, maintained by LSM, to create updating and reformating systems used to maintain these data bases. LSM provided assistance for effective use of the Unified Generator Package.

Plasma melatonin in humans with affective disorders. A. Lewy, J. O'Steen, LCS, NIMH. Daily, round-the-clock measurements of plasma melatonin were taken from patients with affective disorders and normal volunteers. LSM assisted by designing and testing procedures for automatic generation of graphical displays of data, using MLAB.

Test score analysis. A. Lipsky, LPP, NIMH. Scores were obtained from a sample population using the Leyton Inventory Test Scale. LSM designed and tested procedures for automatic generation of graphical displays of data, using MLAB.

Childhood behavior problems. C. Edelbrock, LDP, NIMH. LSM assisted in preparation of 142 graphs displaying clinical data on childhood behavior problems, using MLAB. This data is part of a monograph survey to be published.

Encoding of autopsy reports from an American city. L. Thomas, LP, NCI. Several thousand autopsy reports were automatically encoded by computer into SNOP and ICDO, for a study of the use of autopsy data from a large city (Atlanta, GA).

- Laboratory investigation

Schistosoma Japonicum: Divergence Between Egg Deposition in the Feces in Rabbits Infected with the Japanese and Philippine Strains. A. W. Cheever, NIAID. There has been a renewed interest in the rabbit as a model of Schistosoma japancium infection since it has been demonstrated that in rabbits hepatic vascular lesions are very similar to those in Symmer's fibrosis in man. Eighty infected rabbits, 67 exposed to the Japanese and 13 to the Philippine strain, were examined 8 to 66 weeks after exposure to 50 to 750 cercarial. SAS was used to analysis the data.

Circadian rhythms of protein production in the rat eye. A. Goldman, LVR, NEI. Experimental injections of two radioactive labels into live rats were assessed by separation of retinal homogenate using gel electorphoresis and measurement of product radioactivity by scintillation counter. Labels were injected at different times of day to access circadian influence on production levels. LSM provided assistance in design and testing an MLAB procedure to process scintillation counter paper tapes, perform elementary statistical computations, and generate graphical displays.

Phagosome measurement in the rat eye. A. Goldman, LVR, NEI. Rats were subjected to surgical and drug treatments, to study the effects upon the retinal renewal process. Phagosomes in pigment epithelium tissue samples were counted using light microscopy. LSM provided assistance in design and testing of MLAB procedures to check data base for errors and compute elementary statistical analysis of selected experiments.

Mouse cataract study. P. Kador, LVR, NEI. The "Philadelphia" mouse strain develops hereditary cataracts visible 5 to 6 weeks after birth. In this study, Philadelphia mice were measured for cataract development and lens electrolyte levels were compared to levels in normal controls. LSM assisted with MLAB procedures for processing experimental data and computing elementary statistical measures.

Redox studies of cytochrome. R. W. Hendler, O. H. Setty, LB, NHLBI. LSM is contributing to revisions of a paper on voltage titration of cytochrome spectra, and to biomathematical modeling of an intense, irreversible release of acid from E. Coli membranes under electrical stimulation. Oxygen uptake of reconstituted membranes is also under study, for which LSM provided software and mathematical analysis for digitization and evaluation of strip charts.

Oxygenation of whole blood. R. M. Winslow, IR, NHLBI. Experiments show that pH changes in whole blood can be modeled by simple scaling of oxygen pressure. Imai (JBC 1975) announced that hemoglobin pH does not have this property. LSM is providing biomathematical analysis for appropriate models, to include explanation for experimental findings of nontypical hemoglobin saturation curves.

Hemoglobin saturation analyzer. R. Berger, G. Dossi, TD, NHLBI. LSM is providing biomathematical analysis for design of an analyzer used in measuring biological effects of altitude. Relative concentrations of four states of the oxygen-combining site of hemoglobin are computed by measuring absorbance at several wavelengths and solving related linear equations. A minimum variance technique is being used to select an optimal set of wavelengths. Design criteria require simplicity, accuracy and reliability, for projected uses on a Mt. Everest expedition, in SKYLAB II, and for a study of Peruvian Indians living at 15000 foot elevation.

Regularization of ultracentrifuge data. M. Lewis, BEI, DRS. The applied mathematics of regularization is currently an active field, with many available methods of regularization effective for some cases of the general problem. LSM is advising on the available methods of damping and cross-validation, to design a method tailored for the particular class of ultracentrifuge data obtained by the investigator.

Modeling of Chemical Kinetics. A. Thakur, LTB, NCI. Advice was given on the statistical analysis of chemical kinetics modeling, including the calculation of confidence intervals and tests of hypotheses.

DNA Pattern Matching. M. Bina, NIAID. Consultation was given on DNA string matching to detect regions which are clipped out of the corresponding RNA.

Immunological binding study. J. Dower, NCI. LSM assisted in modeling and curve-fitting data obtained in immunological binding experiments.

Ultracentrifuge data modeling. M. Johnson, CE, NIAMDD. Alternative mathematical models for ultracentrifuge experiments were considered. LSM provided advice on curve-fitting procedures and modeling in MLAB.

Enzyme kinetic studies. J. Harmon, D, NIAMDD. LSM provided advice on modeling and solving differential equations in MLAB, for enzyme kinetics experiments.

Diffusion model. A. Weinstein, IR, OD, NHLBI. A steady-state model of paired differential equations was analyzed. LSM assisted in the analysis and debugging of MLAB procedures for obtaining numerical solutions.

Insulin binding experiments. P. De Meyts, D, NIAMDD. Models of insulin binding with negative cooperativity were analyzed. LSM provided advice on modeling and curve-fitting in MLAB.

- Program management and adminstration

Investigator career profile study. H. Guttman, OD, OPPE, NHLBI. Data on investigators associated with NIH grants have been collected to be used for program management purposes. Included are evaluation of the effects of past NIH-supported training programs, and projections of current and future training programs based upon national needs and currently available researchers. The Unified Generator Package, supported by LSM, has been used to create the software for maintaining this data base and retrieving information from it. LSM provided assistance in the use of the Unified Generator Package, in the use of the generated updating, reformatting, and reporting systems, and in the training of users of the generated systems.

NIH training support. W. S. Batchelor, OD, NIH. Data consists of the number of predoctoral and postdoctoral trainees supported by each Institute, classified by disciplines or medical specialities and by fiscal years. LSM advised on graph-theoretical computations for analysis of this data using MLAB, and assisted in designing and testing a procedure to output the results.

Index's for the DCRT Library Document Collection. E. M. Chu, OD, DCRT. Existing linguistic concordance programs were adapted to produce key word indexes on author and title words of documents which are shelved by an accession-document number.

- Computer research and technique development

SLANG (Structured Language Compiler). R. Magnuson, DMB, DCRT. SLANG is a language processor designed to enable users to write block-structured IBM 370 assembly language source code. LSM assisted in its development by participating in design decisions, detecting errors during the implementation phase, and editing the documentation.

Chemical toxicity study. T. Hopfinger, R. Potenzone, Case Western Reserve University. Clustering techniques relating toxicity to chemical structure were performed. Several small sets of compounds (one including 32 nitrosaminos) showed excellent clustering properties, so that toxicity for a compound of each such class could be predicted from the compound's structure. A set of 385 compounds with diverse structures showed poor clustering properties. LSM provided cluster analysis using C-LAB.

- LSM research projects

Automated Data Processing of Medical Language. M. G. Pacak, LSM, DCRT. Work on further development of a semantically structured medical lexicon to be used for the creation of a medical data base for NCI.

Multivariate Statitical Analysis. J. E. Mosimann, LSM, DCRT. The study of multivariate statistical methods for the analysis of data which take the form of ratios or proportions.

Biological and Visual Shape. H. Blum, LSM, DCRT. Development and application of a new geometry of biological shape which gives a natural and efficient description to a variety of biological objects at vastly different levels of complexity.

Cluster Analysis. M. Shapiro, LSM, DCRT. Research into optimum ways of clustering using the minimal spanning tree algorithms.

Discrete Mathematics and Applications. G. A. Hutchinson, LSM, DCRT. Inclusion relations between vector spaces and related problems concerning modules over rings were studied.

Linear Methods in Statistics. J. D. Malley, LSM, DCRT. Family confidence limits for ratios of sample means from multivariate normal distributions were extended beyond the original unequal covariance data sets.

Nonlinear Equations. R. I. Shrager, LSM, DCRT. Methods are developed for solving nonlinear equations frequently encountered at NIH, usually in the context of constrained nonlinear least squares, or in the solution to nonlinear differential equations.

Research Topics in Computer Science. G. D. Knott, LSM, DCRT. The development of flexible and efficient storage and retrieval algorithms.

Non-numerical programming techniques and applications. L. M. Norton, LSM, DCRT. Using both general purpose and special purpose programming systems, techniques for computer processing of non-numerical data are developed and evaluated by implementing small-to-medium-scale research projects in selected application areas.

Blum, H., and Nagel, R.: Shape description using weighted symmetric axis features. Pattern Recognition, 10:167-180, 1978.

Cole, B. R., Shapiro, M. B., and Rodbard, D.: Chromatography and Electrophoresis Analysis System, in Electrophoresis 78. Elsevier North Holland. 1978.

Habbersett, M. C., Shapiro, M. B., Bunnag, W., Nishiya, I., and Herman, C.: Quantitative analysis of flow microfluorometric data for screening gynecologic cytology specimens. J. Histochem and Cytochem, 27(1):536-544, 1979.

Evarts, R. P., Brown, C. A., and Atta, G. J.: The effect of hydroxylamine on the induction of mammary tumors by 7,12-dimethylbenz[a]anthracene. Experimental and Molecular Pathology, 30:337-348, 1979.

Hutchinson, G., and Czedli, G.: A test for identitites satisfied in lattices of submodules. Algebra Universalis, 8:269-309, 1978.

James, I. R., and Mosimann, J. E.: A new characterization of the Dirichlet distribution through neutrality. Annals of Statistics, in press.

Knott, G. D.: Fixed-bucket binary storage trees. Proc. 12th Hawaii International Conference on Systems Science, 36-48, University of Hawaii, 1979.

Kamel, I. A., Elwi, A. M., Cheever, A. W., Mosimann, J. E., and Danner, R.: Schistosoma Mansoni and S. Haematobium Infections in Egypt. IV. Hepatic lesions. The American Journal of Tropical Medicine and Hygiene, 27:931-938, 1978.

Lieblick, A. K., Symmes, D., Newman, J. D., and Shapiro, M. B.: Development of the Isolation Peep in Laboratory Bred Squirrel Monkeys. The Journal of Animal Behavior, in press.

Marimont, R., and Shapiro, M. B.: Nearest Neighbor Searchers and the Curse of Dimensionaltiy. J. Institute of Math. and Applications, in press.

Mosimann, J. E., and Malley, J. D.: Size and shape variables. Multivariate Methods in Ecological Work, L. Orloci, C. R. Rao, and W. M. Stiteler, eds., p. 17, in press. International Co- operative Publishing House, Fairland, MD.

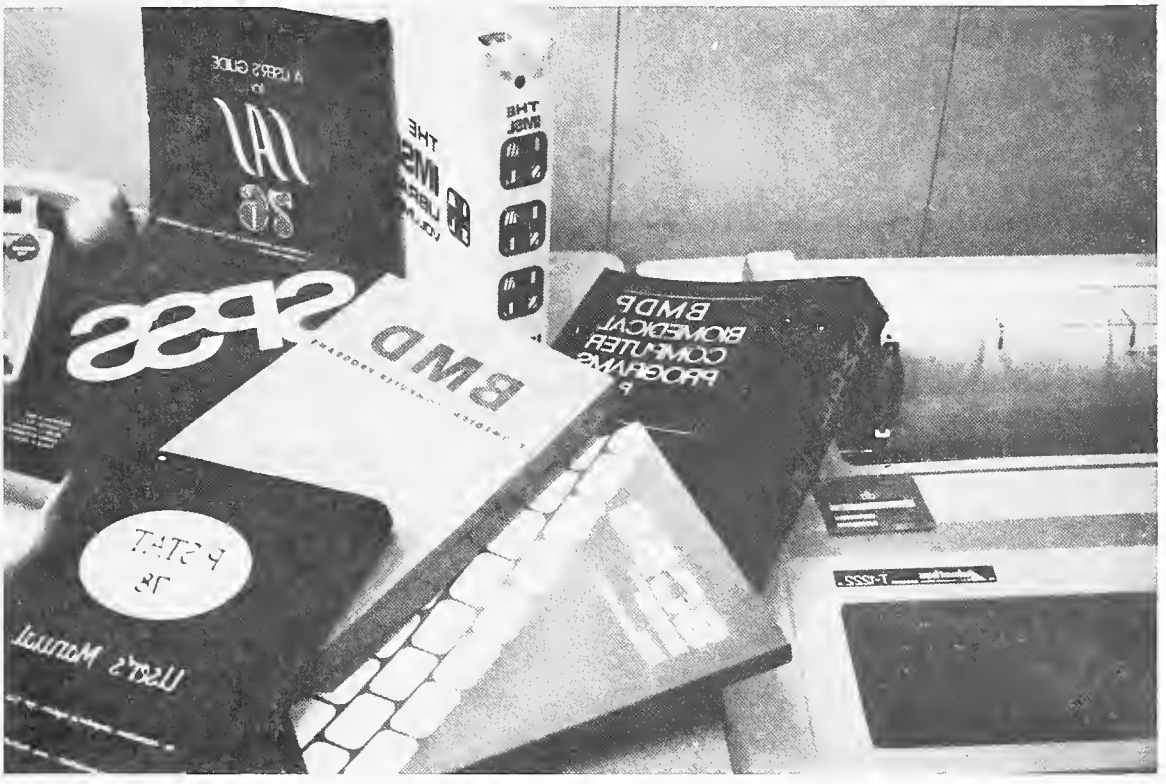
Mosimann, J. E., and James, F. C.: New Statistical Methods for Allometry with Application to Florida Red-winged Blackbirds. Evolution, 33:444-459, 1979.

Mosimann, J. E., Malley, J. D., Cheever, A. W., and Clark, C. B.: Size and Shape Analysis of Schistosome Egg-Counts in Egyptian Autopsy Data. Biometrics, 34:341-356, 1978.

Norton, L. M.: A program generator package for management of data files - the input language. Proceedings, 1978 Annual ACM Conference, p. 217-222, Washington, D. C.

Pacak, M. G., and Dunham, G. S.: Computers and Medical Language. Medical Informatics, 4(1):13-27, 1979.

Webber, R., and Blum, H.: Angular invariants in developing human mandibles. Science, in press.



The use of program packages continues to show considerable increase. The average accesses per month of all the statistical packages rose from almost 9,000 during FY78 to over 12,000 in FY79.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00001-08 LSM

PERIOD COVERED
Oct. 1, 1978 through Sept. 30, 1979

TITLE OF PROJECT (80 characters or less)

Automated Data Processing of Medical Language

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. G. Pacak	Computer Systems Analyst	LSM DCRT
	A. W. Pratt	Director	DCRT
OTHER:	G. Dunham	Computer Programmer	LSM DCRT
	S. Harper	Computer Programmer	LSM DCRT
	M. DeMeyts-Graitson	Guest Worker	LSM DCRT

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Medical Information Science Section

INSTITUTE AND LOCATION
Division of Computer Research and Technology, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The major objective of the project is the continuation of work on further development of a semantically structured medical lexicon to be used for the creation of a medical data base for NCI.

The operational system for information storage and retrieval of pathology data is going to be used for the creation of a medical data base mentioned above. Further improvements of the present encoding system on the morphological, syntactic and semantic level will be studied.

Project Description:

1) Several thousand autopsy reports from Altanta, GA, were encoded into SNOP and ICDO for National Cancer Institute (NCI). Some minor changes in the encoding system to improve its efficiency are under consideration.

2) The computer program for the segmentation and interpretation (paraphrasing rules) was completed for - ITIS forms and is being tested. The program will be used for the development of a generalized system for automated morphosemantic segmentation and interpretation (paraphrasing algorithm) of medical compound words. A similar system is under development for French.

It appears that the utility of automated morphosemantic analysis and corresponding paraphrasing can be adapted for use with other suffix forms such as - ECTOMY - EMIA etc. If so, the lexicon of morphosemantic constituents may become a practical tool for automated processing of medical terminology in English as well as in other languages. It was found that the ratio of similarities in modern national medical languages is very high for medical word forms derived from Greek and Latin. Using the computer as a tool, it might be possible to construct a computer-oriented multilanguage medical lexicon which utilizes these similarities between medical terminologies in different countries.

The program for paraphrasing procedures was written in a modified version of the programming language PROLOG, which was developed at the University of Marseille.

Lexicographic work continued on the construction of a lexicon for pathology. This lexicon was extracted from "Systematized Nomenclature of Pathology (SNOP). It contains parts-of-speech information, and when ever possible, the word is listed with its allomorphs. The goal of the research is to reduce the size of the lexicon and generate automatically linguistic algorithms for processing of morphosyntactic and morphosemantic data which are derived from the microglossary for pathology.

The formal description of a syntactic and semantic parser for medical language data processing is being completed. The parser will be tested on medical data in the near future.

The concordance program was used to create (produce) title and author indexes for the document collection of the DCRT library.

The programming of a frame system for medical linguistic research was completed. Frames are displayed at a CRT terminal from which an operator may select or generate in response. Responses are captured and stored for practical information needs, and responses determine which new frames are called up.

The system has been designed to test the hypothesis that the form (structure and relationships of frames) in which complex data is most easily and naturally elicited from a medical user in a frame system. The system is closely related to the syntax of the noun phrases which are used by the user to express these data in natural language. Collaboration with a clinical research group is being sought.

The tape copies of computer-based medical dictionaries (SNOP, ICDO) were made available to several universities. Their distribution to selected requesters will continue.

Future Efforts:

Continuation of research studies in medical language at present level (morphology, syntax, semantics). Comparative study of structures of computer-oriented medical dictionaries (SNOP, SNOMED, ICDO, SNODERM) is under consideration. Paraphrasing procedures for medical terms derived from Greek and Latin will be tested.

Increased effort to obtain a version of the encoder for implementation on a small computer system.

Testing of frame system on medical data.

Preparation of a tutorial report on logical problems in medical data bases.

Publications:

Pacak, M. G., and Dunham, G. S.: Computers and Medical Language, Medical Informatics, 1979, Vol. 4, No. 1, pp. 13-27.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00012-07 LSM

PERIOD COVERED
Oct. 1, 1978 through Sept. 30, 1979

TITLE OF PROJECT (80 characters or less)

Biological and Visual Shape

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. Blum	Res. Gen. Phys. Scientist	LSM DCRT
OTHER:	M. O'Connor	Mathematician	LSM DCRT
	R. L. Webber	Chief, Clin. Invest. Branch	CIB NIDR

COOPERATING UNITS (if any)

DMG, CIB, NIDR

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
Division of Computer Research and Technology, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.9	0.9	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project develops and applies a new geometry of biological shape that gives a natural and efficient description to a variety of biological objects at vastly different levels: chromosomes, cells, organs, organisms, etc.

Applications are to (1) automation of shape analysis for diagnosis and taxonomy, including those issuing from new devices such as the tomographic scanners, (2) the description and understanding of organ and organismic development, and (3) the psychology and neurosphysiology of shape processes in vision.

Project Description:

The overall objective is to develop a formal descriptive language natural to biological shapes and apply this language to a number of problems arising in main areas of medicine and biology. This would allow for the automation of many shape processes now done by humans and permit better modeling and understanding of these processes for biological and medical purposes.

The methods employed stem primarily from a new geometry conceived by the principal investigator. It is based on the notion of growth as the primitive process. It is being applied to a variety of problems, both to develop new mathematics and computer science in new biologically relevant directions and to uncover and clarify biological processes taking place. The applications include cell and tissue description from light microscopy, shape description of developing cells and organs, chromosome description, visual psychophysics and visual neurophysiology.

New computer capabilities and directions have emerged from this work and continue to do so. A general program for extracting these descriptions is now available at DCRT. The program is currently being rewritten to allow it to be adapted to other computers. The mathematics for extending this geometry to 3-D data, such as will be coming from the variety of new scanners, has been developed to a necessary degree. Computer programs for implementing 3-D analysis are being developed. In addition, mathematics for extracting these descriptions from gray scale data (for example, slides and X-rays) is now being developed. Computer programs for implementing these are also planned.

This geometry has been applied to the study of growth and development of the human mandible. New shape invariants and growth constraints have been found. Results from this work have been submitted for publication.

Publications:

Blum, H., and Nagel, R.: Shape description using weighted symmetric axis features. Pattern Recognition, 10:167-180, 1978.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00008-05 LSM

PERIOD COVERED
Oct. 1, 1978 through Sept. 30, 1979

TITLE OF PROJECT (80 characters or less)

Cluster Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: M. Shapiro Research Mathematician LSM DCRT

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
Division of Computer Research and Technology, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Cluster Analysis and related work has been in three areas:
1. Continual updating of the C-LAB system for Cluster Analysis.
2. Research into optimum ways of clustering using the minimal spanning tree algorithms. Comparison of these methods with standard hierarchical clustering techniques.
3. Initial development of programs and methods for optimum selection of variables in linear regression using branch and bound methods.

Project Description:

Objectives:

The main objective is the development of computer programs and methods for cluster analysis and related problem areas for use by NIH researchers.

Methods:

The development and testing of algorithms based on the latest published research and extensions to it.

Significance to Biomedical Research:

Pattern recognition techniques are now being widely used on biomedical data for classifying objects, finding relationships between variables, and for processing biological images. These applications of artificial intelligence has led to both automatic processing and a better understanding of data.

Proposed Course:

A wider range of Cluster Analysis algorithms will continue to be developed and applied.

Publications:

Habersett, M. C., Shapiro, M. B., Bunnag, W., Nishiya, I., and Herman, C.: Quantitative Analysis of Flow Microfluorometric Data for Screening Gynecologic Cytology Specimens. J. Histochem and Cytochem., Vol. 27, No. 1, pp. 536-544, 1979.

Cole, B. R., Shapiro, M. B., and Rodbard, D.: Chromatography and Electrophoresis Analysis System, in Electrophoresis 78. Elsevier North Holland. 1978.

Marimont, R., and Shapiro, M. B.: Nearest Neighbor Searches and the Curse of Dimensionality. Accepted for publication in J. Institute of Math. and Applications.

Lieblick, A. K., Symmes, D., Newman, J. D., and Shapiro, M. B.: Development of the Isolation Peep in Laboratory Bred Squirrel Monkeys. The Journal of Animal Behavior, in press.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00011-05 LSM

PERIOD COVERED
Oct. 1, 1978 through Sept. 30, 1979

TITLE OF PROJECT (80 characters or less)

Discrete Mathematics and Applications

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. A. Hutchinson Research Mathematician LSM DCRT

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
Division of Computer Research and Technology, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Inclusion relations between vector spaces and related problems concerning modules over rings were studied.

Project Description:

Objectives:

The project objective is to develop mathematical theory and computational techniques using discrete mathematics (algebra, combinatorics and graph theory), and to apply such methods to appropriate problems of biomedical research and computer science.

Methods Employed and Major Findings:

Modules over a ring (a mathematical concept generalizing vector spaces and commutative groups) were studied using the computational methods and algebraic logic reported in previous fiscal years. Some progress was made in extending to related problems the previously-developed computational methods for analyzing inclusion relations between subspaces of vector spaces. A study of the ring similarities which imply that two different rings lead to the same theory of inclusion relations for their modules has progressed. The major finding is that only rings with prime power characteristic need be considered, in order to resolve the problem for arbitrary rings. Both studies above are continuing. Revision for publication of the logical theory described in the previous fiscal year is continuing.

Significance to Biomedical Research and the Program of the Division:

General purpose mathematical techniques and computer programs implementing them are made available to the biomedical research community.

Proposed Course:

Previous work in vector spaces and logic appropriate to algebraic theory will be revised and extended.

A proposed computer science study involving graphical display of mathematically-oriented text and diagrams will be assessed for feasibility.

Publications:

*Hutchinson, G. and Czedli, G.: A test for identities satisfied in lattices of submodules. Algebra Universalis 8, 269-309, 1978.

(*Reported as in press in a previous fiscal year.)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00039-02 LSM

PERIOD COVERED
Oct. 1, 1978 through Sept. 30, 1979

TITLE OF PROJECT (80 characters or less)

Linear Methods in Statistics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. D. Malley Staff Fellow LSM DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Statistical Methodology Section

INSTITUTE AND LOCATION
Division of Computer Research and Technology, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Linear methods in statistics continue to be studied, with the general linear model serving as a point of departure. Family confidence limits for ratios of sample means from multivariate normal distributions were extended beyond the original one-sample result to many-sample equal/unequal covariance data sets.

Also, in the area of the general linear model, extensive study was made of the hazards and appropriate procedures needed for unbalanced data, which is perhaps the most frequently occuring type of data to which the linear model is applied.

Project Description:

The overall objective of this project is the study of linear methods in statistical analyses. During the past year, in addition to family confidence limits for ratios of normal means, and work in automorphism groups and algebras, the linear methods were utilized in the study of log linear models for contingency tables.

Publications:

Mosimann, James E. and Malley, James D. (1979). Size and shape variables. Multivariate Methods in Ecological Work, L. Orloci, C. R. Rao, and W. M. Stiteler, eds., pp. 17 (In press). International Co-operative Publishing House, Fairland, Maryland, U.S.A.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00047-01 LSM

PERIOD COVERED
Oct. 1, 1978 through Sept. 30, 1979

TITLE OF PROJECT (80 characters or less)

Non-numerical programming techniques and applications

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. M. Norton	Research Mathematician	LSM DCRT
Other:	M. G. Pacak	Computer Systems Analyst	LSM DCRT
	M. D. Graitson	Guest Worker	LSM DCRT

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
Division of Computer Research and Technology, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.8	0.8	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Using both general-purpose and special-purpose programming systems, techniques for computer processing of non-numerical data are developed and evaluated by implementing small-to-medium-scale research projects in selected application areas. In the period covered by this report, projects have been initiated in the areas of computational linguistics and differential equations. Programming systems utilized include PROLOG (a language for logic or rule-based programming), REDUCE (a language for algebraic symbolic manipulation), and IBM 370 assembly language (for efficient processing of larger volumes of data).

Project Description:

Objectives:

To provide programming tools for non-numerical data processing and, simultaneously, to obtain research results in applications areas.

Methods:

Programming systems and programming techniques are evaluated by implementing selected research projects utilizing them, thus concurrently performing independent research, and assessing the suitability and effectiveness of the programming systems and techniques.

Major Findings:

The University of Edinburgh PROLOG system for logic and rule-based programming appears to be quite powerful and straightforward to use. It provides a natural context for experimentation with and evaluation of heuristic programming techniques. Application experience in the subject area of computational linguistics has shown that relatively sophisticated routines can be implemented quickly and easily. A routine to analyze and paraphrase compound terms from medical terminology has been developed and is currently being used in a research project. In addition, a particularly powerful form of parser, one for "augmented transition net" grammars, is very readily implemented using PROLOG.

A second research project dealing with word fragments of medical terminology (both English and French) has been implemented in IBM 370 assembly language because of the volume of data involved. As might be expected, the routines are very efficient, at a cost of increased programming time. Both this and the preceding computational linguistics project are not completed yet, but the appropriateness of the programming techniques has been established.

The University of Utah REDUCE system for algebraic symbolic manipulation is being investigated by means of an effort to obtain closed form solutions to ordinary differential equations with constant coefficients using inverse Laplace transforms. This investigation is so far inconclusive, due partly to the inferior nature of the documentation available for the REDUCE system. Productive use of a system such as REDUCE requires the establishment of appropriate mathematical results on which to base computational techniques for symbolic manipulation (just as computational techniques for numerical analysis are grounded in theory involving error analysis, convergence, etc.). As an example, the optimum form of a table of Laplace transforms to be used with REDUCE differs from the form published for manual use. A preliminary version of such a table has been derived as part of this research.

Significance to Biomedical Research:

Development of effective programming techniques for computational linquistics and algebraic symbolic manipulation will make it possible to advance the state of the art in automated processing of medical information, such as medical records, pathology reports, etc., and other biomedical research data.

Proposed Course:

The PROLOG and REDUCE systems will continue to be used and evaluated to determine their suitability for non-numerical data processing, and if suitable, to identify applications on which to use them. Techniques for heuristic programming and for symbolic mathematical computation will be developed and evaluated in the context of these systems. The ongoing computational linguistics projects will be pursued simultaneously for their own sake.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00013-05 LSM

PERIOD COVERED
Oct. 1, 1978 through Sept. 30, 1979

TITLE OF PROJECT (80 characters or less)

Multivariate Statistical Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. E. Mosimann	Chief	LSM DCRT
OTHER:	M. V. Ratnaparkhi	Visiting Associate	LSM DCRT
	J. D. Malley	Staff Fellow	LSM DCRT
	D. R. Ratcliffe	CSIRO, Brisbane, Australia	

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Office of the Chief, LSM, DCRT

INSTITUTE AND LOCATION
Division of Computer Research and Technology, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The overall objective of this project is the study of multivariate statistical methods for the analysis of data which take the form of ratios or proportions.

Multivariate statistical methods (size-shape methods) for analyzing ratios which follow a lognormal distribution have been developed. Exact statistical tests were developed and applied in two biological studies concerning the distribution of schistosome eggs in man at autopsy and morphological measurements of birds. Publications on these studies appeared during this year. Work on the theoretical meaning of size-shape concepts for statistical distributions continued, with an extensive study of the transformations connecting the commonly occuring size and shape variables (Ratnaparkhi, Mosimann, and Ratcliffe). The relationships among the various definitions of size and shape variables in the literature were studied (Mosimann and Malley) and a summary of the relationships prepared (see publications).

Publications:

James, I. R., and Mosimann, J. E.: A new characterization of the Dirichlet distribution through neutrality. Annals of Statistics, in press.

Mosimann, J. E., and Malley, J. D.: Size and shape variables. Multivariate Methods in Ecological Work, L. Orloci, C. R. Rao, and W. M. Stiteler, eds., p. 17, in press. International Co-operative Publishing House, Fairland, MD.

Mosimann, J. E., and James, F. C.: New Statistical Methods for Allometry with Application to Florida Red-winged Blackbirds. Evolution, 33:444-459, 1979.

Mosimann, J. E., Malley, J. D., Cheever, A. W., and Clark, C. B.: Size and Shape Analysis of Schistosome Egg-Counts in Egyptian Autopsy Data. Biometrics, 34:341-356, 1978.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00009-05 LSM

PERIOD COVERED
Oct. 1, 1978 through Sept. 30, 1979

TITLE OF PROJECT (80 characters or less)

Research Topics in Computer Science

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. D. Knott Computer Specialist LSM DCRT

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.4	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Various storage and retrieval algorithms have been studied. The development of flexible and efficient storage and retrieval algorithms is very useful, since such algorithms are used in almost all computer programs. Thus biomedical computation in particular can benefit from improved storage and retrieval methods.

Currently, an exhaustive survey of storage and retrieval methods is underway. This has resulted in several promising hybrid approaches.

Optimal item orderings in split hashing schemes and certain interesting algebraic characterizations of fixed permutation open addressing methods are also being studied. Research on trie methods is also being conducted.

Project Description:

The object of this project is to develop theoretical bases for new computer methods which will expand and improve the use of computing in biomedical computation. The methods used are the application of known algorithms and the development of new pertinent theorems involving combinatoric and other related mathematics. Research work in storage and retrieval algorithms and their efficiency has been the primary topic of concern.

Currently, an exhaustive survey of storage and retrieval methods is underway. This includes the recently introduced k-d tree method. Various improvements and refinements in both the algorithms, and their analysis, are being studied.

Optimal item orderings in split hashing schemes and certain interesting algebraic characterizations of fixed permutation open addressing methods are also being studied.

Research on trie methods, which involves storing items in trees so that the path to the item is determined by its key, is underway as well.

A new hybrid method combining binary storage trees and tries has been developed. This scheme leads to an interesting statistical application as well. This work was reported at a conference this year.

Publications:

Knott, Gary D.: "Fixed-Bucket Binary Storage Trees", Proc. 12th Hawaii International Conference on Systems Science, pp. 36-48, University of Hawaii, Jan. 1979.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00010-03 LSM

PERIOD COVERED
Oct. 1, 1978 through Sept. 30, 1979

TITLE OF PROJECT (80 characters or less)

Nonlinear Equations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. I. Shrager	Mathematician	LSM DCRT
OTHER:	G. D. Knott	Computer Specialist	LSM DCRT
	E. Hill	Mathematician	LAS DCRT
	J. E. Fletcher	Research Mathematician	LAS DCRT

COOPERATING UNITS (if any)
LAS, DCRT

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
Division of Computer Research and Technology, NIH, Bethesda, Md. 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Methods are developed for solving nonlinear equations frequently encountered at NIH, usually in the context of constrained nonlinear least squares or in the solution to nonlinear differential equations. Related problems, such as asymptotic error analysis, and the efficient treatment of sparse systems, are also considered.

Project Description:

Objectives:

To develop methods for solving nonlinear equations frequently encountered at NIH.

Methods:

A continuing effort is made to create methods or extend existing methods to solve problems in a host of NIH applications, and to house those methods in accessible computer programs or routines. Modelaide and MLAB are two examples.

Major Findings:

Two revisions of the paper "Non-linear Curve-fitting in the L_1 and L_∞ Norms", with Edward Hill as co-author, have been submitted to Mathematics of Computation. The revisions involved choosing test problems, making runs, and tabulating results. No new theoretical results were involved. These methods are now coded in SAIL, and a special version of MLAB called OLAB is currently being checked, in which L_1 or L_∞ norms may be used.

There appear to be some cases in which the step size control of the MLAB differential equation solver chooses extremely small steps. Some heuristic is being sought for treating thses cases.

Significance to Biomedical Research:

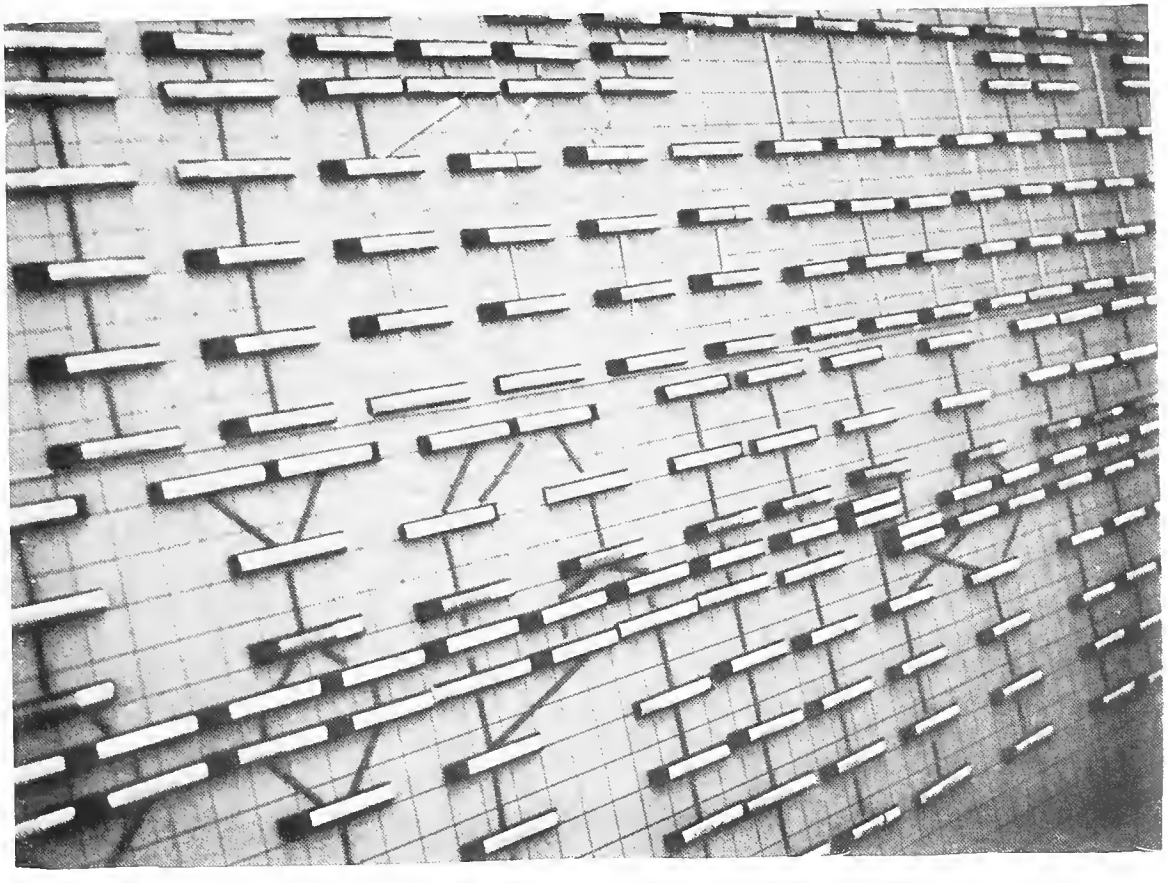
These methods are now being applied to problems in human metabolism, cell growth, chemical kinetics, and spectral analysis (UV, IR, CD, ORD, NMR, ESR).

Proposed Course:

As the methods are proved in test and practice, they will be incorporated into easy-to-use systems like MLAB, and as a result, the systems themselves should evolve to do more useful work with less human and machine effort.

DATA MANAGEMENT BRANCH

J. Emmett Ward
Chief



DMB staff design and create computer-based data management systems for specific users. The above plan reflects the program modules of a system developed by DMB's Applied Systems Programming Section for NHLBI.

I. SUMMARY OF ACTIVITIES

Functions

The Data Management Branch (DMB) provides advice and assistance to research investigators, program officials and administrators throughout NIH in planning for and obtaining computer data processing services. In this role the branch is a central NIH resource for systems analysis, design and programming. There are currently 47 permanent full time employees whose disciplines include computer science, mathematics and statistics.

Scope of Work

DMB staff design and create computer-based data management systems for specific users and train those users. They also teach courses about some data management and programming tools, provide advice on data management techniques to NIH programmers and serve as consultants on implementation by contractors. Finally, DMB creates and maintains general purpose, user-oriented programming tools to speed building and improve operation of specific applications systems.

In FY79 DMB again worked on more than one hundred projects involving virtually every Bureau, Institute and Division of the NIH. Almost 30 percent were projects for applications in patient care, clinical research, or epidemiology; about 13 percent for laboratory research areas; over 41 percent for program direction, management and administration; just over 3 percent for biomedical communications and 13 percent for development of data processing and analytic tools.

About 26 percent of the projects required less than 80 hours each of DMB work and another 42 percent less than 800 hours each. The partial project list in Section II is intended to provide a reasonable sampling of the breadth of DMB involvement in the overall NIH mission. The following items highlight a few areas of particular interest.

FY79 Highlights

As we complete the second full year of our efforts to develop a comprehensive data base for NIH administrative data, the impact on both Materiel and Financial Management has been impressive.

The Materiel Management System (MMS) is capable now of (1) handling all purchases, receiving and payment functions at point of transaction, (2) making all entered data available to all central NIH organizations, (3) providing both regular and exception reports in on-line and batch modes, (4) automatically preparing file reference and reminder information for out-of-sequence events and (5) generating purchase order documents and tracking purchase order number assignments. We have identified several enhancements to the existing system which will be implemented in stages as they are completed during the next four months.

The Central Accounting System (CAS) progress has been a bit slower in its gradual movement toward a data base environment. The primary reason for this is the existing CAS which must be maintained and has required modifications to integrate its processes with the MM data base. The necessary modifications to the existing CAS have been completed. The MMS is automatically generating all relevant obligation, accrual and payment transactions to the CAS and the CAS is capable of processing and feeding back actual payment data to the MMS. During this MMS/CAS integration process we have been able to identify the proposed methodology for handling the CAS data base environment and we are now designing and preparing to implement the first version of a complete MM/CAS data base.

To demonstrate the utility of the data base approach to NIH administrators, a pilot project was implemented with the NCI. This system can track actual obligations-to-date entered in MMS against each basic purchase agreement and indefinite delivery contract. The software was developed for general use and with only minor modification can be used by any program official. Currently the DCRT Information Office is planning a briefing on this system for the AO's.

In July, 1978, the Clinical Support Section hired an unusual computer technician with the understanding that he perform all of his work from his bed at home. Rick Pilgrim is a quadraplegic, who after extensive assistance from the Virginia State Rehabilitation Service learned to program by way of a voice data entry system. When his new section head hired Rick, he also assumed the task of adapting this voice entry system to function with the NIH IBM-370 system.

A collaborative effort between the Clinical Support and the Software Support Sections resulted in a vocabulary, a training program and an interface program which enables Rick's voice communication with the NIH computer facility. Although this effort was initiated primarily for Rick Pilgrim, we are now examining alternative voice entry hardware and potential new applications for this approach.

Immediately after implementing the Cardiology System for the NHLBI in FY78 the benefits of combining its data with that of the Cardiac Surgery System became apparent. Research analyses relating to the same patient or group of patients could be accomplished much more quickly and comprehensively and there also was some potential for a reduction in file maintenance. After obtaining agreement between the Cardiology and Surgery Branches, the DMB created the combined file in early FY79.

On June 1, 1978 the Data Management Branch began full support for the MarkIV File Management System. MarkIV is structured to be used as a function of the system design phase and provides the full range of file maintenance, retrieval, computation and report generation in both batch and on-line environments. The introduction of this system at the NIH should result in a significant reduction in the time required to move from design to actual implementation of complete file management systems for many NIH computer users.

The initial version of a standard package for on-line, interactive scintillation counter data reduction was completed this year and several organizations have already begun to use it. This package, called SCINT, is designed to be used by the non-programmer and can be used as a comprehensive tool for analyzing experimental data. It also interfaces easily with other more powerful systems for analyzing experimental data such as BRIGHT and MLAB. The addition of SCINT complements the standard data logger approach taken by the Computer Systems Laboratory. Thanks to the availability of both techniques scintillation counter users can now record, review and analyze results in an accurate and facile manner.

Future Plans

The Materiel/Financial Management data base effort in the coming year will provide (1) a complete source data entry procedure for basic purchase agreements and indefinite delivery contracts, (2) an invoice entry/accounts payable subsystem, (3) an improved requisition tracking methodology, (4) additional departmental contract information system data, (5) an automatic receiving function, (6) additional data display functions for the BID's and (7) full data base update of open document records for materiel management transactions.

Voice answerback and voice data entry will be studied for possible application to current and future application developments within the DMB.

During FY80, the Clinical Information Utility will (1) expand its data coverage, (2) improve data access, display and analysis functions and (3) be considered for possible interface with other clinical data processing systems.

II. ANNOTATED PROJECT & ACTIVITIES LIST

The list below does not include a number of small new projects and modest revisions and additions to existing systems. These become literally to numerous to mention in an annual report although each is clearly important to the client and requires careful work by the DMB staff.

- Clinical Research, Patient Care, Epidemiology

The Clinical Information Utility System is an archive for data recorded by computers in the Clinical Laboratories of the Clinical Center and by its Medical Information System. The CIU has evolved over the last seven years under the design and operation of the Clinical Support Section, DMB.

The Section made improvements to the CIU during this fiscal year. First, the Bone Marrow and Microbiology Subsystems were redesigned and developed to reduce the costs of both maintaining and retrieving from their data bases. The cost reductions for these operations were approximately 60 percent. Secondly, the CIU Inverted File was expanded. Branch and Institute were added as indices to the file for all the organizations which admit patients in the Clinical Center's Hospital. The expanded indices make it possible for a retrieval to be done by organization, sex, race, test results, body source, specimen and diagnoses. At the request of the Deputy Director of the Clinical Center work began to develop chronological summary reports of all clinical laboratory tests for hospitalized patients.

An On-Line Data Management System for NIMH Patient Care called DMS was completed during the year. DMS programs are general programs which execute under TSO (Time-Sharing Option) on the IBM System 370. The programs are interactive; i.e., they interpret and respond to commands entered by the user at a computer terminal.

DMS is different from many other facilities in several ways: (1) A data dictionary is used to contain all file-dependent information (e.g., variable names, types, lengths, locations, legal values, formats, etc.). Consequently, DMS programs are independent of user files. (2) Programs are available to prospective users to initialize the system without consultation with DCRT personnel. (3) Master files have a direct organization so that records may be accessed individually. (4) User profiles may be defined to restrict access to variables in files.

DMS was designed for data management with small scientific data files. It can be used to enter data, update data, retrieve data, and perform statistics. Data can be entered in free format or fixed format, directly from a terminal or indirectly from a data set. Individual records can be added, changed, or deleted. Data is tested for legality on entry, and all transactions are posted to a log file. Data can be retrieved and listed at the terminal or written to an on-line data set; the conventional arithmetic, relational, and logical operators can be used to define sets of records to be retrieved. Statistics can be performed on-line or in the batch mode using SAS; DMS will set up SAS jobs from specifications entered by the user.

The Cancer Survival System was originally developed in the late 1960's to support the End Results in Cancer studies of NCI. Maintenance and improvement of the system is now the primary goal. Catherine Creede of the Scientific Applications Section is responsible for the continuing support of this system.

A number of operating system related problems which surfaced during the past year were corrected.

During FY79 the system was sent to the College of Medicine at the University of Iowa, the Virginia State Tumor Registry, the Medicare Bureau in Baltimore, Md., and the Department of Statistics at George Washington University.

The data base for Work-Able Cancer Patients Employment Studies, NCI involves pooling of numerous sub data bases prepared by five contractors in different locations for tumor registry. Each contractor data base includes survey questionnaire responses from cancer patients and their employers. Vigorous editing of the data revealed some inconsistencies among contractors with regards to number of options in questions, type of questions asked and type of codes to determine certain values. The contractors were notified and necessary adjustments were made to standardize the data. The process of merging the data sets is underway. During FY80 analysis will be completed to determine variation in patient/employer responses by geographical area.

The Adriamycin Toxicity Study (Analysis of Risk Factors for the Development of Adriamycin (A) - Induced Congestive Heart Failure) was begun in FY77 for the Cancer Therapy Evaluation Program, NCI. Dr. Van Hoff was the Principal Investigator and was supported by Dennis George and Peter Basa of the Documentation and Systems Support Section. During FY79 data entry and initial analysis for U.S. patients was completed. Further analysis of the data precipitated the development of three papers for presentation and publication by Dr. Van Hoff. The system was used to provide information in both tabular and graphic form for dosage levels and schedules of administration by age group, sex and race. Dr. Van Hoff left the NIH during the FY and anticipated future work may be delayed on this project pending agreements between him and the NCI.

Reports were produced to provide initial analysis of designated risk factors such as previous cardiac diseases, tumor type(s), therapy (adriamycin and/or concomitant drugs/radiation) and patient condition at start of adriamycin treatment.

In FY78 the Cardiology Branch Data Processing System became operational. Prior to that the Heart Surgery Branch Data Processing System had been operational for a few years. It became apparent that the heart surgery and cardiology data were complementary and involved the same processing approaches. It was therefore decided to develop a Combined Cardiology/Heart Surgery Data Base. This would provide a complete chronological record of activity of NHLBI Cardiology and Heart Surgery Branch patients. This effort involved logically merging the two data bases and developing and implementing computer programs that duplicated the capabilities of the two separate systems but provided the advantage and simplicity of a single system and data base. Retrievals from the common data base are enhanced since selections can now be logically based on both surgery and cardiology data. The combined system became operational in FY79 and has proven to be an asset to NHLBI physicians and researchers.

In support of the Applied Systems Programming Section in FY79 for the Cardiology System, John R. Parks of the Software Support Section created tailored generator software. Special versions of TRANSACTGEN and REPORTGEN were written permitting generation of many source COBOL subroutines.

Giant Foods is conducting a "Foods for Health" program in cooperation with NHLBI. Stores in Washington participating in the program are being compared with a control group of stores in Baltimore to see if customers' buying habits are changing in response to the campaign. Data for fourteen food groups are being analyzed. Diane Feskanich, Scientific Applications Section, has developed a method of reformatting the data as recorded on tapes received from the stores and preparing it for input to a time series/analysis of variance program. She has produced summary statistics and scatter plots which provide a visual representation of buying habits over time.

During FY79 the Analysis of Systemic Lupus Erythmatosis (SLE) Nephritis Patients System was developed to store chemistry and therapy data on all SLE patients. These patients participated in the Arthritis and Rheumatism Branch studies of SLE, from November 1968 to present. Patient data is stored by categories; i.e., Dating of Clinical Manifestation, Therapy, Objective Information, Lab Data, Complications, etc. Each category of information contains sub-categories of information. For example, under the "Objective Information" category, the sub-categories include: skin biopsy, parotid flow rate, lip biopsy, parotid scan, brain scan, bone marrow, etc. The system also allows multiple entries of all items.

The clinical chemistry data, urine data and the hematology data for each participating patient are supplied by the Clinical Support Section.

A subsystem was designed and implemented to format and verbally describe the content of each patients' updated file. This provides an easily available reference for doctors.

Analysis is underway on a group of patients with SLE participating in the immunosuppressive trials and assigned to receive either prednisone only or the combination of prednisone and cyclophosphamide. The variables that will be examined include serum creatinine, creatinine clearance, 24 hour proteinuria, DNA binding and C'3.

Throughout FY79 George Roberts of the Applied Systems Programming Section has worked closely with Dr. Knowler in the Southwest Field Studies Section, NIAMDD, to systemize the several separate steps involved in his analysis of increased incidence of retinopathy in diabetic patients with elevated blood pressure. The Diabetic Retinopathy Data Analysis System has been quite successful and the procedure is being examined to determine if it can be expanded to evaluate more and different variables from different data files.

The Study of the Incidence and Prevalence of Kidney and Urinary Tract Diseases in the Armed Forces was begun in 1974 for the Kidney Disease Program, NIAMDD, to evaluate the occurrence, morbidity and mortality of kidney and urinary tract diseases in an effort to determine research needs. The principal investigator is Dr. Nancy Cummings. The project leader for the system is John A. Haggerty, Jr. and the principal programmer is Darius Georg of the Documentation and Systems Support Section. Data for the study was made available by the Air Force, Army and Navy. There has been difficulty in obtaining correct data from the Army. We received our fourth set of data from the Army during FY79 and ran a series of reports. The data involved additional diagnosis codes and covered the years January, 1971 through June, 1977. The original data requested was for the period of January, 1971 through December, 1973. Present plans are to prepare reports using the Army data, After this is completed a decision will have to be made to either request the additional data from the Air Force and Navy or eliminate the additional data received from the Army when comparing data for the three services. Evaluation of reports prepared using Army data are being made by Colonel Hodder of the Army who has become a collaborating principal investigator of the study.

The Kidney Transplant Histocompatibility Study was organized in 1972 to determine the efficacy of tissue matching in human kidney transplants. The primary objective of the study is to examine the relationship between HL-A matching and the success of renal transplantation. Since August, 1974, the Biometrics Division of the Naval Medical Research Institute has, under contract to NIAID, served as the Statistics and Data Management Center for the study. Some preliminary analysis of the data has taken place. The study is in the process of being transferred from the Naval Medical Research Institute to the NIAID. In November of 1978 a KTHS Data Analysis Protocol was prepared, which at present, lists 48 proposed areas of analysis. These are to be performed by means of frequency tables, actuarial life table analysis, and multivariate analysis based on application of the Makeham model developed by Drs. Homer and Bailey of NMRI and included as a procedure in the Statistical Analysis System. Catherine Creede of the Scientific Applications Section is involved in the programming support of the analysis mandated by the protocol.

In collaboration with Dr. Eugene Harris, Chief of the Laboratory of Applied Studies, DCRT, George Shakarji conducted an analysis of a set of data from a 1975 Study of Chemistry Data from Survey Participants by the College of American Pathologists. Analysis of variance and non-parametric ranking tests were conducted on calcium, glucose and chloride test values to determine trends among survey participants.

In collaboration with Dr. Eugene Harris, Chief of the Laboratory of Applied Studies, DCRT George Shakarji continued work on the Use of Statistical Models of Within-Person Variation in Long-Term Studies of Healthy Individuals. This included analysis of 14 biochemical and 7 hemotological test values obtained from 115 healthy men and 47 healthy women who participated in a community-wide program of biochemical profiling and health surveillance in San Francisco.

In an effort to determine patterns, forecast ranges were computed using statistical models to evaluate the validity of projected hypotheses. Trend data among tests were also compared to determine whether consistent patterns were detectable.

In collaboration with Dr. Eugene Harris, Chief of the Laboratory of Applied Studies, DCRT, George Shakarji conducted the Temporal Changes in the Concentration of Serum Constituents in Healthy Men: Distributions of With-in Person Variances and their Relevance to the Interpretation of Differences Between Successive Measurements Study. The study involved 37 healthy males, aged 23 to 57 years, each of whom contributed 19, 20 or 21 weekly blood specimens (mean 20.2) during a five month period. Long-term analytic variation was eliminated by storing the serum specimens at -20 degrees C and then analyzing them all together in a single run on a Vickers M-300 multi-channel analyzer. Analytic variance within the run was monitored in a conventional manner. The data base comprised approximately 7400 assay results.

During FY79 programs were written to perform time trend analysis using the mean-squared successive differences approach. While models have been developed to define patterns of the data, unexpected fluctuations have occurred. We are now attempting to both determine the causes of and predict a pattern for these fluctuations.

In collaboration with Dr. Eugene Harris, Chief of the Laboratory of Applied Studies, DCRT, George Shakarji examined the Use of the Population Distribution to Improve Estimation of Means in Epidemiological Studies. The properties of some statistical calculations which would help to improve the accuracy of observed values in clinical trials as estimates of the true values of individuals. The procedure is simply that of replacing the observed value by its weighted average with the group mean.

The Empirical Bayes' approach, applied in this study, aims at improving the accuracy of estimating an individuals true value by a weighted average of a single measurement of the individual and the mean of such measurements over the entire group of individuals sampled.

At the request of Dr. Griff Ross, Deputy Director of the Clinical Center, work began to develop chronological summary reports of all clinical laboratory tests for hospitalized patients. Dr. Ross (right) explains his need to reduce the size of medical records through computerization, to DMB Clinical Support Section Head William Vincent.

- Laboratory Investigations

The In Vitro Information System (IVIS) was developed to process information about In Vitro carcinogenesis tests conducted under the auspices of the Division of Cancer Cause and Prevention of the National Cancer Institute. The sponsor was Dr. Virginia Dunkel and the principal investigator was Mary Linhart. Joseph Campbell of the Software Support Section designed the system. The system provides for the collection, maintenance, analysis and reporting of In Vitro data. Data for the system will come from contracting laboratories on input forms with both descriptive and results data. The input forms will be converted into machine readable format and be processed on the Division of Computer Research and Technology (DCRT) computing facility using the proprietary MarkIV system installed in February, 1978. Development of a system using MarkIV was completed and turned over to the user during FY79. The MarkIV system was also used to develop and implement the mammalian study for the NCI and was turned over to the contractor during the year.

In FY79 the Clinical Studies Section in the Laboratory of Viral Carcinogenesis, NCI asked the Data Management Branch to analyze their current data processing capabilities and approaches to see how they could be improved upon by way of a newly designed computerized Seroepidemiology Data Processing System.

Judy Mahaffey of the Applied Systems Programming Section assumed responsibilities for the study. The results of the analysis along with a recommended systemized approach to regaining control of the data processing and making the data much more accessible and usable was presented to NCI in the form of an analysis report/proposal. The report/proposal was well-received and the system design ideas accepted. It is anticipated that Mrs. Mahaffey will be responsible for implementation of the major portion of the proposed system.

Late in FY79 the Data Management Branch was asked to design a computerized Wild Asian Mouse Breeding Colony Data Processing System for maintaining data for a facility which breeds and raises a rare, valuable strain of wild Asian mice originally acquired in Vietnam. The system is being designed for the Laboratory of Viral Carcinogenesis, Division of Cancer Cause and Prevention, NCI by Vivian Pelham of the Applied Systems Programming Section. The system will maintain virtually all data collected on the animals. Information from the system will aid in mate selection, etc. The system is at present in the initial design phase. Development will continue into FY80.

The Genetic Marker Tracing System for the Laboratory of Immunogenetics, NIAID, involved the analysis, design and creation of a system to provide the capability for tracing genetic markers within a colony of rabbits. The principal investigator for the system was Dr. John Sogn, LIC/NIAID; the Documentation and Systems Support Section with Dennis George as project leader and Jane Blessley assisting, provided the analysis, design and creation of the system which was turned over to the user during the year.

The Data Management Branch was asked by the Veterinary Resources Branch, DRS in the Poolesville Installation to design a computerized Canine Breeding Colony Data Processing System to assist that facility with their record keeping and work scheduling. The proposed system should produce many reports to be used by VRB personnel to help them with their daily work. The project was taken over by Roger Dailey of the Applied Systems Programming Section. Pre-design analysis has been completed and a design proposal is being prepared.

The Reproduction Research Branch of NICHD employs various physical/chemical methods of protein separation in its work. It is possible to obtain, across time, quantitative data on the position, bandwidth, peaks, etc. of the proteins under study. In January of 1977, work began on the Chromatography and Electrophoresis Peak Analyzer System for automating the analyzer of this data.

Working closely with Dr. David Rodbard, RRB, Brian Cole of the Scientific Applications Section developed an interactive system for fully automatic peak detection and characterization, non-linear curve fitting of overlapping Gaussian distributions with an exponential baseline, quantitative measuring of the resolution between any two peaks for optimizing the conditions of resolution, and cut-point purity and yield projections useful in preparative fractionation. All this has been designed into a program which can interface with a non-computer oriented user, with a degree of automation and ease and convenience of operation never before achieved in a peak detection program.

During FY79, this system (designated "CEPHAS") has been enthusiastically received by a growing number of research scientists at NIH and copies of the system have been sent to researchers at MIT, Texas A&M, the University of Washington, Boston University Department of Chemistry, Baylor College of Medicine and the University of Maryland. Dr. Rodbard with Mr. Cole's assistance, has written an article which illustrates the value of the computer system, to be published in the international technical journal STERIODS.

Now that a data logger is available to standardize liquid scintillation output for easy input to the computer, Brian Cole, of the Scientific Applications Section, is developing on the PDP-10 the Liquid Scintillation Counter Package System which can answer the needs of a reasonably large percentage of scientists who use liquid scintillation counter reduction.

During FY77-78 Mr. Cole produced a working version of an interactive self-teaching system which handles most of the problems encountered in Chromatography and Electrophoresis. It provides both simple, fast graphs of experimental results at the user's display terminal or teletype (for quick review and as an aid in planning the next phase of an experiment), and high-quality graphs produced offline by the computer center's Calcomp plotter (suitable for publication). During FY79 work has been completed on expanding the system to provide channel-ratios, dual-label experiment calculations and other basic scintillation counter reduction.

Documentation for the system was completed and the system was announced to the users of the NIH PDP-10 in April, 1979. Several people at NIH have successfully used at least some portion of the system. People consulted during the development of the system have been contacted again to assess the need for further development of the system at this time. Mr. Cole is currently in the process of training new users of the system.

- Administrative and Program Management

In 1978 when the Data Management Branch began the New Developments in the Central Accounting System they assumed responsibility for the NIH Central Accounting System; two areas were identified to immediate attention. System testing required use of the production software to verify accuracy of new additions or changes to old procedures and there was no standard document for the year end processing procedure. Both of these areas left the maintenance team and the system unnecessarily vunerable to error.

In FY79 the Financial Support Section (FSS) designed and established a small test model of the Central Accounting System (CAS). Test system master files were created from a representative sampling of the various types of records in the CAS. Current CAS report programs have been modified and catalogued to provide step by step reporting of the actions of the test system. The test system provides the Financial Support Section with the ability to fully test proposed changes and additions to CAS without interrupting the on-going activities of the financial management at NIH.

The Financial Support Section prepared a manual to be used as a basic reference for personnel involved in the fiscal year end closing of the NIH Central Accounting System. The manual contains a calendar of events to occur each day with notations describing special handling. This calendar can be reused year after year with only minor changes. The sequence of events does not change. It also has chapters to describe each of the processes required at year end. Each chapter contains a narrative description of the process and the programs to be executed. There are also file descriptions, run and restart instructions and modifications, if necessary from year to year.

The Financial Support Section (FSS) received over 30 requests from the DFM for Modifications to the Central Accounting System to modify processing and to provide new or modified reports. The FSS collaborated with the Program Support Section, CCB, in identifying potential areas for improvement in daily, weekly and monthly procedures. Each of the recommended improvements were analyzed and, where feasible and reasonable, were implemented. In addition, the FSS reviewed its requirements for improved maintenance and use of on-line (dedicated), card and tape storage facilities. This review resulted in several modifications which improved both the maintenance function and the efficiency of daily processing. A summary of these activities follows.

Recurring production jobs were reworked to save on cost and time and to eliminate the possibility of errors. This process included:

(1) Changing the blocksize of files to reduce required dedicated disk space.
(2) Combining functions of two programs into one program.
(3) Reordering steps in the jobs according to files being used.
(4) Replacing tapes with on-line disk space for passing data between steps.
(5) Renumbering the steps in the jobs using unique and meaningful numbers.

When the laser printer became available, a study was conducted by The Division of Financial Management and the Financial Support Section to determine current reporting needs. It was decided that the daily status reports should be printed on the laser printer. Other reports to be kept for historical purposes were to be produced on microfilm or microfiche. The number of hard copy reports was greatly reduced. In FY79 we changed 3 reports to microfilm, 25 to microfiche and 26 to laser printer. This effort significantly reduced the special handling required for CAS output.

The Financial Support Section addressed several other problem areas in the Central Accounting System and made the following modifications.

(1) Setup our own procedure library.
(2) Put programs on WYLBUR under project initials and thus eliminated the need for punched card maintenance.
(3) Established use of DSSUBMIT to get jobs run without conflict.
(4) Replaced parameter cards with one parameter data set for all steps within a job.
(5) Arranged to have Treasury accept labeled tapes from NIH.

Some other changes to the CAS were:

(1) Added Vendor data base to CAS where needed to verify EIN's. Removed the file GEN.VENDOR and all references to it.
(2) Added an output file to CAS to report to the Materiel Management System all payment activity.
(3) Added Wylbur data set to the monthly travel system programs to permit the Division of Financial Management Travel Section to flag travel advance records on which they have received repayments not yet posted to the CAS.
(4) Reformatted the two column vendor name and address report to three columns.

The Office of the Secretary, DHEW, requested that the NIH provide Special Reports From the Central Accounting System for a study on commissions. This required a review of all obligations and disbursements made with CAS since FY73. The Division of Financial Management (DFM) requested assistance and Clare Hoover of the Financial Support Section assembled information from the historical tape files of the CAS and produced the necessary disbursement reports. Several additional reports were provided to DFM to verify the reported information. A system for Quarterly Reporting of transportation payment data to the General Services Administration was designed for the Division of Financial Management by the Financial Support Section and implemented starting with the first quarter of the fiscal year. The system provides DFM with a file containing the total amount of payments made on Transportation Schedules by NIH to each Employer Identification Number (EIN) during the quarter being reported. Two reports generated by the system help the Division of Financial Management staff to answer questions from carriers concerning payments which were made to them by NIH and to combine records on the payment file if two EIN's in CAS equate to one carrier.

The Financial Support Section is responsible for providing an Interface between the Materiel Management System and the CAS at NIH. At the beginning of FY79, MMS was generating transactions to record obligations in CAS. By the end of the year CAS was also processing commitment, accrual and payment transactions from MMS and work has been started on projects involving advance payments, partial payments and an invoice entry system.

During FY79 the Central Accounting System (CAS) was modified by the Financial Support Section to accept accrual and payment transactions from the Materiel Management System (MMS). In addition several other modifications were required to (1) duplicate the timing of the on-line MMS system in the CAS batch processing mode, (2) notify MMS of payment and other transactions which bypassed it for various reasons and (3) accept commitment transactions as a function of end of month reporting.

Verification of accurate processing was provided by the new CAS test system and all integration appears to be functioning well in the production mode.

The Financial Support Section reviewed the specifications for batches of transactions from MMS to verify that the values of the data elements within the records were compatible with the demands of CAS. The CAS Test Model was useful in this review.

The Materiel Management Billing System provides a method for billing service and supply fund users for their Materiel Management service charges. It runs at the beginning of each month using the CAS Monthly History files from the previous month as input. A billing tape is created covering Central and Self-Service Stores, contracts and small purchases. The system creates and updates year-to-date files containing number of procurement actions, total dollar value of procurements and dollars charged for processing these actions. Six reports are generated by the system for use by the Service and Supply Fund staff and some for distribution to the BID's.

There have been frequent small changes to the system this year. Service and Supply Fund management has requested that the system be run, to reflect activity thru the 22nd of each month. It will be necessary to change the source of information used to run the system and some programs will have to be changed.

The Materiel Management System is a computer based NIH-wide system designed and implemented for the NIH Office of Administration by the Data Base Applications Section in collaboration with the Data Base Administrator, DMB. The project leaders are Marvin Katz and Ron Wicks.

The system operates primarily in an on-line environment utilizing data base management technology, namely IBM's Information Management System (IMS). In addition to the on-line functions, the system provides for periodic batch-processing functions to meet operational, accounting and management control requirements.

FY79 saw significant expansion of the Materiel Management System. Phase I, procurement control, successfully went into production last year. In early February Phase II was placed into operation. This phase permits on-line entry of receiving data as well as the capability of processing requests to produce reports in support of order payment. The total cycle from order entry to receiving and finally payment was thus completed with the flow of accrual and disbursement transactions to the Central Accounting System.

An exception reporting system was also implemented to improve control of operations in the receiving and accounts payable areas. Included in these reports is the automatic generation of overdue receiving letters to the vendors.

The principal analyst/programmer for the Materiel Management System (MMS-Query and Reports) is Jane Blessley of the Documentation and Systems Support Section. The original goal of this project was to determine the feasibility of using MarkIV as an economical alternative to IMS Inquire for reporting information from the MMS data base. MarkIV has proven to be very cost effective when compared to Inquire. Currently, MarkIV is used to provide most of the ad hoc reports produced from the MMS data base as well as 11 daily, 5 weekly and 3 monthly reports. In addition MarkIV is also used to provide MMS data to the Contract Information System, Document Numbering System, Requisition Tracking System and the BPA/IDC Balance System. Future plans to optimize the production of reports from the MMS system will involve the use of MarkIV in combination with other programs.

During FY79, Catherine Creede, Scientific Applications Section, completed the Workload Statistics System which provides an analysis of the workload of the Accounts Payable Section, DFM. The workload statistics programs provide a number of tabular reports which display quantities, equivalent units and man-hours for 15 types of invoices received and processed by APS during a monthly period. These reports are statistical analyses by work-station, team, unit, section and commercial unit. In addition to the printed reports, a new balance table is produced which is used as input to the next month's run. DFM may run reports monthly, weekly and on request.

Ronald Edwards of the Scientific Applications Section wrote the Leave Liability Reconciliation program to generate information needed to reconcile the general ledger unfunded accrued leave and reserve for leave liability for annual leave and compensatory time against the subsidiary civil service and commissioned officers records. The Division of Financial Management will run the program on an as needed basis. Results are recorded on microfiche.

Darius Georg of the Documentation and Systems Support Section is working with the principal investigator, Dr. Rhode of the O/D office in developing the Bioscientists Information System to create and maintain files of information on people qualified to serve as members of NIH's Initial Review Groups (IRGS) etc. This information will be used by the Office of the Director and other BID's.

The principal analyst/programmer for the Committee on Academic Science and Engineering (CASE) Reports project is Darius Georg of the Documentation and Systems Support Section. As a result of the recommendations of the CASE, these reports have been produced annually since 1965. The reports are prepared for the Division of Research Services, Office of Program Planning and Evaluation (OPPE). They summarize DHEW awards to Institutions of Higher Education, Health Professional Schools, Non-profit Hospitals, Non-profit Research Institutes and Operating Foundations, and Research and Development Centers. The data for FY79 has all been received, edited and balanced, and copies sent to the National Science Foundation (NSF). The program developed during the last fiscal year to match previous years data with the incoming data was used on all data this year and proved to be very successful in that a number of reporting component organizations were alerted to gross discrepancies and were able to recheck their records and either resubmit new or amended data. Final reports should be completed during this fiscal year.

Darius Georg of the Documentation and Systems Support Section developed the System for Controlling and Monitoring Complaints of Discrimination at NIH for the Division of Equal Opportunity. The data base contains information on formal and informal complaints of discrimination at the NIH to: (1) provide statistics associated with processing complaints in a more timely fashion and (2) enable the user to more closely monitor status of complaints. The system was implemented during the year for formal complaints.

The Office of Program Analysis, DRR, requires an Integrated Information Management System for handling program data. In FY79, DRR requested a complete systems redesign. They would like more capabilities than the original design allows (e.g., interactive querying, plots, etc.) plus a more manageable update/retrieval scheme, better correlation of scientific and administrative data and shorter response time for filling requests.

Sigurd Knisley of the Scientific Applications Section, began the overall systems analysis last year. During FY79, systems design and implementation have been pursued. A number of data handling systems were explored and MarkIV was selected as offering the best combination of capabilities for solving DRR's information handling needs. Meetings have been held with DRR program managers to determine their specific requirements and retrieval specifications have been written for those reports which have been identified. The file structures have been devised and data elements defined. Conversion from the old "Integrated Management System" format to MarkIV format was done. MarkIV retrievals based on the converted files have been supplied.

Plans for FY80 include supplying report capability for coordinated files, exploration of interactive retrieval and design, and implementation of data collection capability.

The computerized Review and Evaluation Branch Grants Information Processing System was designed and implemented for the Division of Cancer Grants, NCI, by Penny Brogan of the Applied Systems Programming Section. The effort has extended over a four year period. The system provides for (1) data input from IMPAC and CRISP as well as data entered by RAEB, (2) file maintenance for extramural funded and unfunded grants and contracts, (3) several reports and (4) flexible retrievals which make it possible to select on scientific codes as well as on many other variables.

With knowledge gained through her experience with the NCI RAEB system, Mrs. Brogan has been able to consult with and advise two other institutes on improving their internal grants and contracts management systems.

Peter Basa of the Documentation and Systems Support Section provided analysis, design and implementation of a computerized Rental Information System to replace the DRS manual inventory control and accounting system. The purpose for establishing the system is to provide better control of rental equipment inventory and more timely reports. The system has been operational since early FY79.

The initial phase of this automated Survey of Biohazardous Materials System for DRS was designed to print a questionnaire that was sent to all of the NIH labs. Data was collected for each employee who is working with any biological agents, tissue cultures, etc. listed in the questionnaire. An on-line data collection program has been written and tested. All reports requested were completed during the year. This project was done by John A. Haggerty and Charles Twigg of the Documentation and Systems Support Section for the Principal investigator, Dr. John Irwin of ESB/DRS.

Charles Twigg of the Documentation and Systems Support Section is working closely with both the sponsor, Mr. Ralph Van Wey of the OD/DRS Office and the principal investigator, Mr. Zoon of the RSB/DRS. The Radiation Safety Control System for DRS will be composed of the following subsystems:

(1) Inventory and Bioassay
(2) Training
(3) Laboratory Survey and Airborne Release
(4) Waste Processed and Activity Balance
(5) Film Badges

The total system should be an integrated system capable of supplying data from one subsystem to another in order to produce desired reports.

The analysis and programming for the Inventory and Bioassay subsystem has been completed. The system was put into production as of March 1, 1979.

Analysis and programming of the training subsystem will not proceed until the Inventory and Bioassay subsystem has become operational. The Laboratory Survey and Airborne Release/Waste Processed and Activity Balance subsystems have not yet been defined.

- Biomedical Communications

In FY79 the Library Circulation System, designed by Judy Mahaffey of the Applied Systems Programming Section for the Division of Computer Research and Technology Library, became operational. The system provides the DCRT Library with a computerized method of inventory control. This in turn helps to improve circulation and monitor usage of "individual" items. The system pays particular attention to accuracy and status of circulation items, usage statistics and generation of overdue notices.

The Scientific Applications Section has continued support of the current awareness search for Chemical Biological Activities (CBAC). The Selective Dissemination of Information (SDI) Service is still offered free of charge to all researchers at NIH and is run bi-weekly as tapes are received from Chemical Abstracts Service in Columbus, Ohio. Retrospective requests are being referred to the on-line service, TOXLINE, available at NLM.

DMB continued support of the current awareness search of Biosciences Information System (BIOSIS). Three times a month tapes are received from the Biological Abstracts Service and information is disseminated to the NIH community thru the same vehicle as CBAC.

The Reference and Bibliographic Services Section of the NIH Library has been the primary contact with the NIH researcher wishing to search this data base; profiles are submitted through the library to DMB for current awareness searching, and to NLM for retrospective searching.

As the data base suppliers updated their tape formats and added new data elements for searching during FY79, Sigurd Knisley made the necessary changes to the system programs.

- Computer Research and Technical Development

During the year the Clinical Support Section developed a Voice Recognition and Response System which is used by a handicapped programmer to write digital computer programs. When a speaker makes an utterance the speech is digitized and the result is compared with all known digitized speech patterns in the minicomputer. If a match is found the character set associated with the utterance is inserted into a line of programming code. Once the line of code is completed, it is transmitted to the Central Computer System for storage and further processing.

In FY79 the Voice Input Compiler, designed by Robert A. Magnuson of the Software Support Section became operational. Rick Pilgrim's program for voice input to WYLBUR was written using this compiler. This is an RMAG implemented compiler that works with the Interstate Electronics Voice Data Entry System. The user is permitted true symbolic entry which is compiled into the rigid, absolute format required by the Voice Data Entry System.

In FY79 the SLANG (Structured Language) Compiler, designed by Robert A. Magnuson of the Software Support Section became operational. Designed to assist programmers writing powerful structured programs for the IBM 370, the SLANG compiler generates block structured assembly language code. An extremely efficient machine language program, SLANG is coded in itself.

In FY79 the Project RMAG: Arithmetic Subroutine, designed by Robert A. Magnuson of the Software Support Section had new features added. Two new operators, JDAY and JDATE, were implemented. These permit powerful date calculations involving the current calendar system.

In FY79 the Project RMAG: Symbolic Logic Retrieval system, designed by Robert A. Magnuson of the Software Support Section had new features added. Users can now have upper and lower case descriptions in their history files. Also the inclusion of the JDAY and JDATE operators in the AR relations permit powerful date calculations involving the current calendar system.

In FY79 REPORTSLR, designed by John R. Parks of the Software Support Section became operational. This is a special version of REPORTGEN that gives SLR (Symbolic Logic Retrieval) users flexible report generation capability.

In FY79 REPORTGEN, designed by John R. Parks of the Software Support Section had new features implemented: (1) Added use of RMA31 file read subroutine which provides the ability to read edit format files and files with RECFM = F, FB, V, VB, or U. (2) Error handling improved. (3) Added use of RMA20 (Arithmetic Subroutine) to provide JDAY/JDATE calculations.

In FY79 the entire staff of the Software Support Section provided necessary support for the many and varied section products. This support included program maintenance, customer assistance and the teaching of formal DCRT courses on these products. The supported products included RMAG, SLR, Logic Subroutines, Arithmetic Subroutine, SLANG, REFORMATGEN, REPORTGEN, TRANSACTGEN, Standardized Update, Voice Input, IRS and MarkIV.

III. PUBLICATIONS

Cole, B.R., Shapiro, M.B. and Rodbard, D.: Chromatography and Electrophoresis Analysis System (Cephas): Computerized Peak Detection and Characterization. In Catsimpoolas, N. (Ed.): Electrophoresis '78. New York, Elsevier-Holland, 1978, pp. 79-92.

Harris, E.K. and Shakarji, G.: Use of the Population Distribution to Improve Estimation of Individual Means in Epidemiological Studies. In J. Chron. Dis. Great Britain, Pergamon Press Ltd., 1979, pp. 233-243.

Rodbard, D., Cole, B.R., Murakami, T., and Strott, C.: Computer Analysis of Concentration Profiles: Automated Peak Detection, Characterization, and Estimation of Molecular Size. Steriods, 1979.

COMPUTER CENTER BRANCH

Joseph D. Naughton
Chief

Oliver Morton, Harriet Weltman, and others staff the PAL (Programmer Assistance and Liaison) Unit, which handled 19,750 calls or visits for user assistance during the year.

I. SUMMARY

Functions

The DCRT Computer Center Branch designs, implements, and operates the NIH Computer Center, a powerful network of modern computers and communication facilities. The nucleus of this network is composed of two large multi-computer subsystems, the IBM System 370 and the DECsystem-10, each having unique capabilities. Communications facilities link these two subsystems and connect them by telephone lines to terminals of various types located in research laboratories and administrative offices throughout NIH. The computing and communications equipment (systems hardware) are controlled, balanced, and complemented by a very complex set of computer programs (systems software) designed and implemented by the Center or acquired from other sources and adapted to meet the requirements of the NIH research program.

Services and facilities provided by the Center include a variety of programming languages (e.g., FORTRAN, COBOL, PL/I, SAIL, Assembly Language), a data base/data management system (IMS), and a comprehensive library of utility programs. For users with terminals there are also interactive systems such as WYLBUR, TSO, and the timesharing services of the DECsystem-10, which facilitate creation, submission and output of jobs and permit direct interactive computing (using FORTRAN, BASIC, CPS, APL, MLAB and other languages). The Center also provides many facilities for the output of textual and graphic information on paper and microfiche. Programs to show two or three dimensional pictures on cathode ray tube displays and "sketch pads" for advanced graphic projects such as involving macromolecular structures are available.

This network of computers and variety of services are provided by the 139 members of the Computer Center Branch. Making the total system function smoothly requires professional, technical and administrative support people. The (51) professional people include computer specialists, programmers, and system analysts with widely varied backgrounds, including biophysics. The members of this group provide the expertise to design and implement the complex computing systems. They provide extensive training and information services, and assist users in problem diagnosis; they also maintain and schedule recurring production applications. The (78) technicians operate the computer systems and plotters and provide data entry services. The remainder of the staff provides the necessary administrative support.

Scope of Work

The Computer Center operates the NIH Computer Utility 24 hours a day, providing services to over 6,000 users, including research scientists and program managers from all NIH Bureaus, Institutes, Divisions and offices. Twenty-nine other Government agencies use these services.

During the past year, the IBM System 370 Facility continued to grow, exceeding the previous year by 10%. (Figure 1 is a chart of workload growth since 1967.) At the year's end the Center was handling over 430,000 tasks per month. This includes 10,000 mainstream jobs a day processed by the Utility, with 80% of them completed within one hour. The source of many batch jobs were the 5,200 interactive sessions per day conducted from some 1800 remote terminals.

The DECsystem-10 use grew 10% over the previous year (Figure 2 is a chart of use since 1972). This growth has nearly saturated the CPU capabilities of the system, causing degraded response at times. The 14,000 user sessions per month used 14,000 connect hours resulting in the use of 400 CPU hours per month.

Research continues in the areas of: text editing, application utilization of mass storage devices, display of biomedical objects, computer networking, and communications.

Highlights of the Year's Activities

The highlight of the year was the establishment of the Computer Center's general purpose facility as a Federal Data Processing Center for Biomedical and Statistical Computation. The agreement to become a Federal Center was made under the authority given to GSA by Congress to establish computing centers that take advantage of equipment pools and allow multi-agency sharing. Such sharing enables small and new agencies to have immediate access to a wide range of tested, specialized computing techniques at reasonable costs. The NIH users of the Center also gain since the sharing brings with it significant cost advantages usually reflected in lower rates for computing services. Sharing of computer resources enables other agencies to benefit from software developments at NIH for similar computational needs.

A mass storage device was delivered late in the year. The mass storage will solve several of the Computer Center's operational problems and will lead to a comprehensive, hierarchical data storage system to meet the diverse demands of the Computer Center users.

The Computer Center completed its drive to provide the NIH user with better interactive terminals. Two types of hardcopy terminals were selected to augment the NIH7000 CRT terminal. One new terminal, the Alanthus T1222, is a matrix printer that operates at 120 characters per second. It can be used as a standalone terminal and will function with any NIH terminal system. This terminal has the added feature that it can be configured to provide hardcopy output for the NIH7000 CRT. The second terminal, the CleanType 45, is a "quality print" hardcopy terminal. It operates at speeds of either 30 or 45 characters per second and can produce very legible output in a variety of type fonts. These selections complete a three year task of specifying, negotiating and selecting interactive terminals that best fit the needs of biomedical research and its administrative support.

Effective, fast, data processing is always a function of online data storage. Throughout the past few years, space to store online data has been a scarce commodity. During the past year, new disk drives were installed on the DECsystem-10 that provided a 33% increase in online data storage. At the same time, the disk units on the 370 were modified with the effect of doubling the capacity of public online data storage. This extra capacity linked with the mass storage facility should satisfy the NIH demand for data storage.

The popularity of the Computer Center Training Program led to an extensive reorganization of the program. The main thrust was to make training available on a year round basis, thus providing more convenient times for students. There are now four three-month sessions per year rather than two four-month sessions. The self study and audio visual courses were expanded into additional areas in an effort to broaden the scope of courses offered to users.

The surface display of the Computer Center Branch graphic system improved its sphere-drawing algorithm. Scientists are now able to draw 10,000 to 15,000 atoms in one pass, instead of the previous limit of 1800 atoms. The success of the surface display for macromolecular research is evident: over 10,000 stereo images were drawn last year, many for publication.

After several years of intense negotiations, the GSA and NIH came to agreement about the contents of the RFPs for replacement of the DECsystem-10 and System 370 equipment. As the year ended, the DEC-10 RFP was about to be released and the System 370 document was being commented upon by industry through the pre-release mechanism.

Future Plans

The second floor of Building 12B finally became available for Computer Center personnel occupancy. The long delayed reconstruction of the second floor of Building 12 and the first floor of Building 12A began. The reconstruction projects will provide additional modern, physically secure space for computers and new user output areas featuring locked boxes as well as improved security for output.

New WYLBUR remains on the horizon. It was hoped that it would reach the users this year but early next year is a more realistic date. The final sections of the document preparation modules are being debugged. The documentation is nearing completion and the final software and hardware plans needed to insure a smooth transition from Old to New WYLBUR are being finalized.

The coming year will see the facilities of the newly-arrived mass storage unit offered in multiple ways to the user. Eventually, the mass storage and the software developed for it will handle online data sets, small data sets currently on magnetic tape, and migration. A hierarchical data storage system will become a reality with this device.

For some time, the Computer Center has been operating page printers that produce output of consistently high quality. The full capabilities of this device will be offered to users in the upcoming year. Expanded character sets, user provided character sets, forms design, and forms flashing are the more important features that will be introduced.

The past year saw the installation of a digitizing densitometer. Extensive work on the software for the system should be completed and the densitometer put into production during the coming year.

The Computer Center will complete a major telecommunication advance early next fiscal year. A very comprehensive study of the NIH Computer Center communications needs was followed by a complete survey of the state of the art communications equipment that would meet the Center's needs. The equipment envisioned had to have improved switching capability, substantial capacity for growth, diagnostic testing facilities and coherent design flexibility to adapt to new and innovative data communications services. An "all data" Centrex system was selected. Final cutover to the new switch is scheduled for December, 1979. At that time, the old stepper switch that has served NIH for ten years will be retired. All data communication services will then be centralized on the new Centrex switch designed for data traffic, the first switch ever designed for this purpose. The new Centrex switch will provide the Computer Center with greatly improved reliability and more cost effective data communications.

Because of the great interest in the surface display system, a number of unsolvable macromolecular structure problems were proposed by various collaborators. The focus of the problems seems to be on the need for an integrated energy minimization capability. This problem area is still in the analysis stage and should emerge into programming and experimentation at the beginning of the next fiscal year.

In order to bring the results of the macromolecualr surface display system to the largest possible audience, an information dissemination project similar to the AMSOM atlas has been planned and is in the implementation stage. When finished, this project will provide teachers of biochemistry with a tool for the stereoscopic presentation of the structural aspects of proteins and nucleic acids.

Most important to NIH, the coming year should bring the results of the RFPs written for the selection of new equipment for both the DECsystem-10 and the System 370. Selections and awards may be made and possibly late next year the first of the next generation hardware will arrive and be put into productive use. With the award of the contracts, the Computer Center will be able to concentrate on offering the users improved tools for biomedical and statistical computing as well as the finest in turnaround and support.

DECsystem-10 Improvements. DECsystem-10 users finally got relief from the online disk storage shortage when new, higher capacity disk drives were installed. These new drives will provide a 33% increase in public data storage capacity.

SAIL, one of the more popular programming languages for the DECsystem-10, was enhanced. The new facilities included improved random access facilities, new packages to handle input/output, software interrupts, interprocessor communications and non-blocking input/output.

Use of the link between the DEC-10 and 370 was such that a second link between the systems was installed. The number of files transmitted has more than doubled. CLINK, the communications link from the DEC-10 to small laboratory computers, was further improved to handle a wide range of laboratory computers. Over 1,000 usages per month were recorded for CLINK.

The DECsystem-10 announced the availability of PASCAL. PASCAL was designed so that simple, powerful and consistent rules encourage the programmer to create structured programs with few errors. One important feature of the language is the ability of programmers to create data types. The compiler further checks that the types are being used in consistent ways and thus many errors are spotted.

The task of generating finished books, manuals, papers, letters and other documents was simplified with the introduction of PLUTO - an easy to use documentation language. The system includes commands for document sectioning, creating tables of contents, footnotes, one and two level indices and cross referencing. Hyphenation, chart generation, formatted and quotations are also available. PLUTO will allow even the novice to produce finished documents with a minimum of effort.

System 370 Improvements. The Center's users benefited when performance monitoring showed that region size could be increased without adversely affecting performance. The region size was doubled to 1 million bytes for all job classes. The new region size will permit larger programs to be run without segmenting or use of overlays.

The third and fourth IBM 3800 page printers were added to the system. They will allow the system to handle the increased output on standard 8-1/2 x 11 inch paper. But more importantly to the user, there is sufficient capacity to allow the Computer Center to announce and support additional capabilities of the page printer. Additional character sets, user defined character sets, and special forms will be offered to users by the end of the year.

The scarcity of online storage space was alleviated as the disk drives were updated. The online public space was doubled in size. The Computer Center hopes to keep ahead of user demand by proper use of the online disk space combined with the installation of the mass storage system.

A step forward in the area of data security was taken with the announcement of new tape data integrity protection facilities. The new facilities reduce the incidence of problems such as accidental overwriting of tape data sets and assure that jobs access only tapes whose use is properly authorized by the owner of the data.

Terminal Improvements. Two new hardcopy terminals were made available and delivered to users. Culminating a three year effort, a high speed hardcopy terminal and a quality hardcopy terminal were selected and deliveries to users started during the year. The user now has a complete range of terminals available for his use at the NIH Computer Center.

Rate Reductions. The fiscal year started with a 10% rate reduction offered by both systems. Additionally, the night time discount rate for 370 services was increased to 35%. System utilization kept increasing (some of it no doubt caused by the rate reductions) faster than the projected growth rate. This led to the second rate reduction of the year. In May 79, the 370 system reduced its batch processing rate by an additional 20% to $.80 a machine unit, and increased its night time differential up to 50%. The DECsystem-10 reduced its basic charge an additional 17% to $1.25 a machine unit. Also, the DEC-10 night differential was doubled to 50% and extended to include Saturdays and Sundays. Terminal connect time for the DEC-10 was reduced 1/3 to $2.00 per hour. The economies of scale and continuing growth both contribute to reduce the cost of biomedical and statistical computing at the NIH.

Procurement. After years of intense negotiating with GSA, several RFPs were launched or are about to be launched. An RFP resulting in the selection and award of a contract for the mass storage device was completed late in the year. The RFP for the replacement of the DECsystem-10 was released to the vendors late in the year. The RFP for the replacement of the 370 reached a significant milestone as the document entered the prerelease stage, that is, industry was asked for comments on the RFP before its formal issuance.

User Education and Assistance. The Computer Center training program was extensively reorganized during the year. Instead of two four-month terms per year, four three-month sessions were offered. This made training available year-round and provided more convenient times for many students. Self-study courses were expanded to include audio visual courses and computer assisted courses. Applications for training during the year numbered 1317, but only 889 of these could be accepted. There were 64 sessions of 37 different courses given during the year.

The theory that by educating the user you increase his understanding and reduce his problems, was fortified by the fact that Programming Trouble Reports researched and answered during the year decreased to 2300. User Services also applied over 4200 system fixes during the year and installed 35 new releases of current software packages. There were 19,750 calls or visits for assistance during the year.

The Technical Information Office maintained its high level of responsiveness to users with the aid of a newly automated user profile system operating under IMS. There were 79,000 individual pieces of technical documentation in support of the NIH Computer Utility mailed to the 6,080 users registered for the automatic documentation service. An additional 5,574 requests for documentation were satisfied in response to over-the-counter and telephone requests.

III. PUBLICATIONS

Feldmann, Richard J., Bing, David H., Furie, Barbara C., Furie, Bruce: Interactive Computer Surface Graphics Approach to study of the Active Site of Bovine Trypsin, Proceedings of the National Academy of Science USA, Vol. 75, No. 11, November 1978.

The Computer Center operates the NIH computer utility 24 hours a day. Computer operators like Robert Harris (center) provide services to over 6,000 users including research scientists and program managers from all NIH Bureaus, Institutes, Divisions and offices.

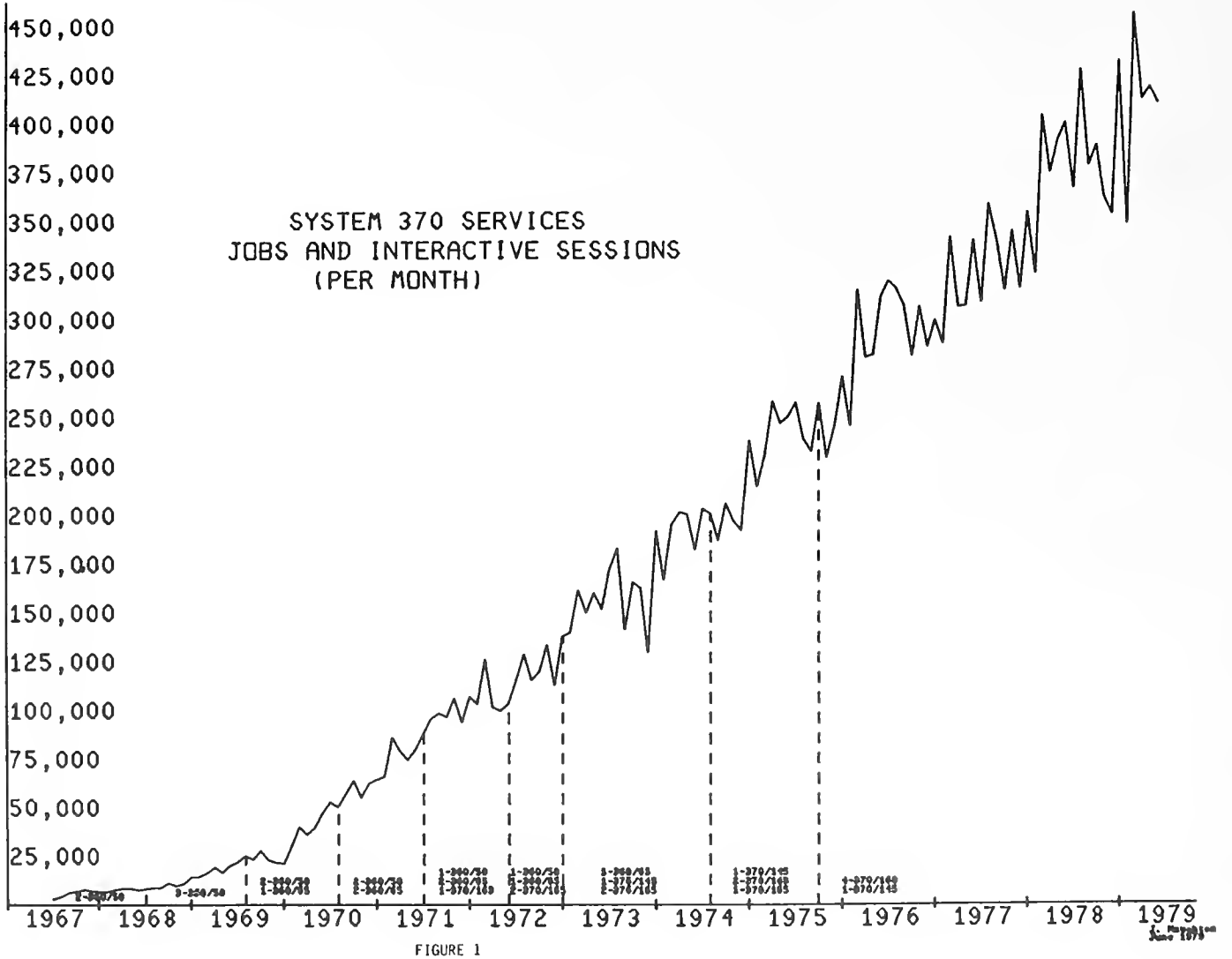

SYSTEM 370 SERVICES
JOBS AND INTERACTIVE SESSIONS
(PER MONTH)
450,000
425,000
400,000
375,000
350,000
325,000
300,000
275,000
250,000
225,000
200,000
175,000
150,000
125,000
100,000
75,000
50,000
25,000
1967
1968
1969
1970
1971
1972
1973
1974
1975
1976
1977
1978
1979

FIGURE 1

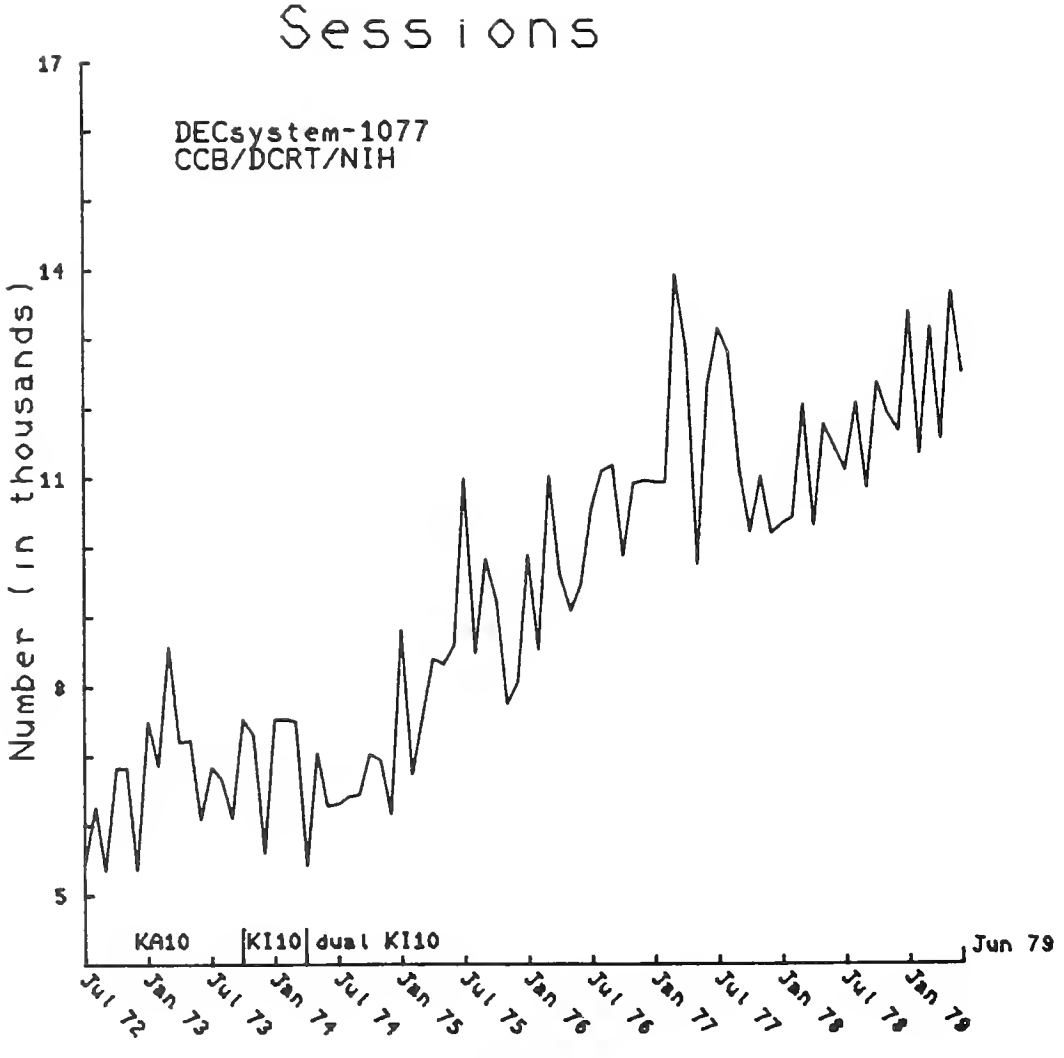

Sessions
DECsystem-1077
CCB/DCRT/NIH
Number (in thousands)
17
14
11
8
5
KA10
KI10
dual KI10
Jun 79
Jul 72
Jan 73
Jul 73
Jan 74
Jul 74
Jan 75
Jul 75
Jan 76
Jul 76
Jan 77
Jul 77
Jan 78
Jul 78
Jan 79

FIGURE 2

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00036-03 CCB

PERIOD COVERED

TITLE OF PROJECT (80 characters or less)

Graphic System for the Display of Biochemical and Biomedical Objects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Richard J. Feldmann, CCB, DCRT, Computer Specialist

Others: Thomas K. Porter, CCB, DCRT, Computer Specialist
Charles R.T. Bacon, CCB, DCRT, Computer Specialist

COOPERATING UNITS (if any)

None

LAB/BRANCH

Computer Center Branch

SECTION

INSTITUTE AND LOCATION

DCRT, NIH, Bldg. 12A, Room 3009, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.25	1.25	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Implementation of graphics system for the respresentation and manipulation of biochemical objects is being done at various levels of hardware, system software and user software. Work on the link between the DECsystem-10 and the graphics system was brought to completion. Modifications to the surface generation algorithm resulted in the removal of a limit of 1800 displayable atoms. The system can now do hidden sphere calculations for between 10,000 and 15,000 atoms. Programs were developed for the interactive modeling of up to 300 atoms at a time. Modeling of larger structures is handled by scooping out sections within the 300 atom limit. This programs have been applied to the modeling of drug-protein interactions and drug-nucleic acid interactions.

Implementation of a digitizing microscope densitometer is proceeding slowly at the system software and hardware testing levels.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00046-01 CCB

PERIOD COVERED

TITLE OF PROJECT (80 characters or less)

Dissemination of Macromolecular Surface Representations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Richard J. Feldmann, CCB, DCRT, Computer Specialist
Others: None

COOPERATING UNITS (if any)
David R. Bing, Center for Blood Research, Boston Mass.

LAB/BRANCH
Computer Center Branch

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bldg. 12A, Room 3009, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Collaboration with NIH and NIH-supported scientists has showed that macromolecular surface representations, which are generated on the Surface Display system are very important in understanding molecular function. The clearest perception comes from looking at the images in stereo. After using the Surface Display system for about one year and looking at a number of macromolecule, it seemed that the images could be used by a large population of biochemists. A stereo sample was developed and sent out. The response to the sampler was very strong. Comments came back that these stereo images would be an important tool in teaching the relationship between macromolecular structure and function. A search was made for a medium of presentation and the result was an inexpensive stereo viewer. The stereo images for the student are formatted 7 per card and the package will have 7 cards. The teaching unit will consist of 100 stero slides of which 7 x 7 = 49 for the students are a subset. Depending on user response, we will consider doing other, perhaps more specific, packages in this medium.

PUBLIC HEALTH SERVICE - NATIONAL INSTITUTES OF HEALTH

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Report of Program Activities

October 1, 1977 through September 30, 1978

ANNUAL REPORT

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Page

PHYSICAL SCIENCES LABORATORY

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

October 1, 1977 - September 30, 1978

DIRECTOR'S SUMMARY

During FY'78 the laboratories and branches of the DCRT again carried out their several, complementary functions very well:

- The Physical Sciences Laboratory advanced its research on mathematical theory and practical instrumentation to explain biological phenomena in term of chemistry and physics at the subcellular molecular levels.

- The Laboratory of Applied Studies extended its collaborative projects with scientists, at NIH and elsewhere, with particular emphasis on clinical research applications, centering around mathematical models of function in health and disease.

- The Laboratory of Statistical and Mathematical Methodology had increased use (more than 12,000 calls per month) of the statistical program packages it supports for NIH and received more requests for consultative help in statistics, mathematics and computer science.

- The Data Management Branch continued its widespread support to scientists and administrators throughout NIH, working with the staff of about 80% of the B/I/Ds during the year; DMB also undertook important new responsibilities in support of some central NIH administrative systems.

- The Computer Systems Laboratory embarked on several new projects developing mini and micro computer systems for NIH laboratories and clinics and with the Computer Center Branch it developed new communication links from these kinds of systems to the central NIH facilities.

- The Computer Center Branch helped more people (some 6,000 registered users) to do more work (over 4 million accountable jobs) at lower rates on improved NIH central computer systems.

The reports of the DCRT laboratories, branches and offices are self-contained and speak for themselves. A copy of the detailed FY'78 announcement of DCRT computer resources provided for NIH scientists and administrators is enclosed with this annual report to complete the archive. There are several long-term trends worth noting in those reports.

First is the continued growth of computing throughout NIH laboratories, clinics and offices. This comes from the addition of some new users each year and from the refinements made by existing users to make fuller use of their existing computing applications. In many cases these refinements take advantage of advances in hardware or software technology.

Second is a growth of intellectual linkages among the DCRT staff and their counterparts in the programs of NIH and other research organizations. The result is better communication between the DCRT staff and those organizations and better use of computing in those programs. One facet of this phenomenon is the new Advisory Committee on Computer Usage established by the NIH Deputy Director for Science early in FY 1978. But more important is the growth in the number and productivity of research projects that cross disciplinary and organizational boundaries.

The third trend is a growth in administrative complexity of computing in a Federal agency. The General Services Administration has mandated competitive reprocurement of both the DEC System-10 and the IBM 370 segments on the central NIH computer facility. The GSA has also limited the NIH ability to upgrade existing systems with newer, less costly, more effective equipment prior to the competitive reprocurement.

The result will be at best some delay in obtaining the benefits of new technology for thousands of NIH users of the central systems. The worst case could be a return to the circumstances facing NIH in 1965, when it began to convert all of its computer software to entirely new kinds of computers. It is difficult to predict accurately the effect on NIH of any conversions among the markedly more complex computer systems of the late 1970s.

Three other events in FY'78 may also influence the course of the reprocurement of central NIH computer systems. The Office of Assistant Secretary for Management and Budget, DHEW, unilaterally initiated the purchase of some of the IBM 370 hardware currently leased by the NIH Computer Center. The ability to upgrade the existing NIH central computing resources will be even more sharply limited during the recompetition and prior to the installation of new hardware.

In April, the General Accounting Office published a report titled "The Federal Information Processing Standards Program." This exhorts the President, the OMB, the GSA and the Secretary of Commerce to tighten up the Federal standards program. There are supposed to be 29 such standards; only 10 of these have been developed since 1965. A burst of Federal activity to develop new standards over the next year or two may confuse or confound the NIH computer reprocurement as it moves forward during that period.

Finally, a study of Federal data processing undertaken as part of the Administration's Reorganization Initiatives in the OMB is now coming to completion. It, too, is reported to recommend various new actions. Many people expect Representative Jack Brooks to hold hearings on the study.

The prospect for computing at NIH is therefore one of guarded optimism. The trends within DCRT and NIH toward better computing and better communication about and understanding of computing are encouraging. They can improve the record of excellence created over the last decade. The effect of the trends elsewhere, in the GSA, GAO, OMB and other parts of DHEW, will certainly complicate life for the DCRT. It remains to be seen whether they will detract from the quality of computing at NIH.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT

2. OFFICE OF SCIENTIFIC AND TECHNICAL COMMUNICATIONS

3. William C. Mohler, M.D.
Chief

I. SUMMARY

Function

The DCRT office of Scientific and Technical Communications, under the direction of the Associate Director, DCRT, includes:

- The DCRT Library, which maintains a special collection in computer science and mathematics, statistics, engineering, information science and management. The library directly supports DCRT activities and is a resource for other NIH staff. It also functions as an integral part of the local Washington area network of special libraries.
- The DCRT Information Office, which serves as the focus for the Division's program to provide information about DCRT activities to the rest of NIH and to the public.
- Scientists assigned to this office, working on research and development projects in biomedical data bases, image processing and decision analysis.

Highlights of FY78 Activities

The DCRT Library continued approximately the same level of circulation services for its DCRT and NIH users as in previous years. It had an increase in the number of requests for interlibrary loans and for the first time lent more than it borrowed from other libraries. The Copyright Law that went into effect in January required changes both in interlibrary loan operations and in record keeping and notification for photocopying at NIH.

Use of automated information retrieval services increased slightly. The Library currently has access to 29 data bases for direct searching. The addition of 17 data bases from BRS this past year has increased our coverage considerably. MEDLINE, Computer and Control Abstracts, and OCLC have been the most heavily used. These data bases are available through the National Library of Medicine, Bibliographic Retrieval Services, Inc. (BRS) and OCLC through membership in FEDLINK. The Library is also a registered user to order individual searches with the NASA Information Center, Defense Documentation Center (DDC), and the Smithsonian Science Information Exchange (SSIE).

In the middle of FY78 the library staff began work with the DCRT Data Management Branch on design and implementation of a new automated circulation system.

The new system will include features to improve library services. The most important feature will be automatic data checks for inconsistent and erroneous terminal input. The system will also save time in updating the records of circulating materials and in generating overdue notices and reports. A new feature will be collection of statistical data on all monographs and documents to facilitate timely purchase of multiple copies to assist in weeding considerations of seldom used materials.

The process of creating this system included a complete review of cataloging on all library monographs, as well as creation of input records for the master files. This large task was aided by two temporary summer employees.

During FY78 the DCRT librarian served as the Federal Representative to the Metropolitan Washington Library Council, a member of the Executive Board of the Interlibrary Users Association of the Washington/Baltimore area, a member of the NIH Library Committee, a member of the Federal Library Committee of the BRS users group and a member of the FEDLINK/OCLC Executive Advisory Committee. She was editor of the IUA Directory and Subject Index in FY78.

The DCRT Information Office continued the progress begun in FY77 under its new Information Officer, but in the middle of the year Mr. Hudson accepted the call to become the full time minister of his church. The major emphasis during FY78 was on creation of new printed materials telling about DCRT activities and the resources available to aid NIH scientists and administrators.

The scientific staff was increased by the return of Martin Epstein from an assignment at the Medical School of the University of California, San Francisco. Dr. Prewitt, who received her Ph.D. from the University of Uppsala in FY 78, continued her work with Dr. Wu on new methods for image processing, pattern recognition and decision analysis. She was a consultant and advisor to several NIH Institutes and Divisions and to other Federal Agencies, particularly the National Science Foundation. She was also very active on IEEE committees on Image Processing, worked on the Board of Directors of the Biomedical Engineering Society and served as editor and reviewer for several publications in the field of biomedical image processing.

Dr. Mohler reorganized the NIH Clinical Elective for Medical Students on Computers in Clinical Medicine which had not been given since 1974.

Future Plans

The activities of the office will continue along the lines followed in FY78.

The Library plans to cope with its "space problem" by gradually converting some of its journal holdings to microforms. This substantial increase in its microform collection will require purchase of a microform reader/printer. When file construction for the new automated circulation system is complete, the library will create a new set of printed indices for its document collection and will consider the prospect of converting the card file for monographs to a printed format.

Plans for new activities in the Information Office are awaiting recruitment of a new DCRT Information Officer.

Mr. Epstein will pursue the work he carried out in California on the design and implementation of clinical research data bases with emphasis on interactive "natural languages" query systems to make them more usable by clinical scientists.

Dr. Prewitt's plans for the work on biomedical image processing and decision analysis include a larger effort on the collaborative projects in development of criteria of malignancy for breast tumor cell aspirates and bladder cancer tissue sections.

Project List

1. PEEP/DECIDE/GRAPH. J.M.S. Prewitt, S.C. Wu, OSTC

   PEEP/DECIDE/GRAPH is an interactive programming system written in SAIL, the Stanford Artificial Intelligence Language, and operating on the DCRT PDP-10 computer. PEEP is designed for picture processing applications, DECIDE is intended for algorithmic decision-making and exploratory data analysis, and GRAPH has capabilities for two and three dimensional graphics. PEEP/DECIDE/GRAPH has been implemented as a single system with a large library of image processing, feature extraction and decision-making algorithms. We are maintaining it for public use as well as using it for our own research on blood cells, breast aspirates and bladder epithelium.

2. Characterization of Breast Aspirate Cells. J.M.S. Prewitt, OSTC; B. Stenkvist, J. Holmquist, Uppsala.

   This long term collaborative project to analyze and characterize all images from human breast aspiration biopsies has identified the utility of four analytic features (nuclear length of major axis, density and entropy) as distinguishing among five all type categories in breast aspirate material stained with Papanicolau Stain. Studies are in progress with materials using other stains.

3. Bladder Cancer Tissue Analysis. J.M.S. Prewitt, S.C. Wu,

   The long term study of nuclei in bladder tissue was reactivated in FY78. Preliminary studies were made on two sets of tissue.

4. Tumor Growth Curves. J.M.S. Prewitt, OSTC

   Previous work on a generalized tumor growth curve equation was extended during FY78.

5. Natural Language Access to Clinical Data Bases. M.N. Epstein, OSTC

   The objective of this project is the development and evaluation of a system that will allow physicians access to medical data through natural language queries to support both patient management and clinical research.

A prototype system has been implemented for a small data base on malignant melanoma. The physician can input queries in English that retrieve specified data for particular patients or for groups of patients satisfying certain characteristics, that perform simple calculations, that allow scanning of the data base, and that assist in identifying relationships among attributes.

6. DCRT Library Circulation System. E. Chu, Librarian

Examination in FY77 of alternative hardware/software improvement to the old system led to decision to redo it using the NIH Computer Center facilities rather than as a stand-alone system. The Librarian and DMB staff designed and implemented the new system The Library staff are in the process of putting the data into the master files.

7. DCRT Information Program.

This project, begun in FY77, developed several new brochures describing DCRT activities, set up distribution rack in the new Building 12A lobby. The project halted temporarily when the Information Officer switched careers in the middle of FY78.

Publications

Chu, E. M.: (Ed): Interlibrary Users Association Directory and Subject Index. Washington, D.C., Interlibrary Users Association, 1978, 43pp.

Epstein, M.N., and Kaplan, E.B.: Criteria for Clinical Decision Making. In Schneider, W. and Sagvall-Hein, A.L. (eds.): Computational Linguistics in Medicine. North-Holland Pub. Co., 1977, pp 35-44.

Prewitt, J.M.S.: Some Applications of Pattern Recognition and Image Processing to Cytoloty, Cytogenetics and Histology. Doctoral Dissertation, Department of Computer Science, Uppsala University and Department of Clinical Cytology, University Hospital, Uppsala, Sweden, April, 1978.

Prewitt, J.M.S.: Reconstruction Software for Computerized Tomography. Proceedings of Computer Software Applications Conference 1977, IEEE Press, 1977, pp 285-292.

Prewitt, J.M.S.: Interactive Decision-Making for Picture Processing. Proceedings of the 1977 IEEE Conference on Decision and Control. IEEE Press, 1977, pp 373-379.

Prewitt, J.M.S., Barber, A. and Wu, S.C.: An Application of Pattern Recognition to Histology. IEEE Computer Society Conference on Pattern Recognition and Image Processing. Chicago, Illinois, June 1978, pp 499-506.

Prewitt, J.M.S., and Mendelsohn, M.L.: Analysis of Cell Images. Reprinted in Machine Recognition of Patterns, A.K. Agrawala (Ed.) Wiley, New York, 1977, pp 362-280.

Wu, S.C., and Prewitt, J.M.S.: Deriving Concavities from the Fourier Coefficients and Its Role in Pattern Recognition. Proceedings of the 30th Annual Conference on Engineering in Medicine and Biology, 1977.

Wu, S.C., Prewitt, J.M.S., and Lehman, J.: To Extract a Connected Object of Arbitrary Shape from its Background by Decision Tree Method. IEEE Computer Society Conference on Pattern Recognition and Image Processing. Chicago, Illinois, June 1978.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT 00030-03 0STC-0

PERIOD COVERED

October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Applications of PEEP/DECIDE/GRAPH

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Judith M.S. Prewitt, Ph.D.
S.C. Wu, Ph.D.
Dr. K. Kent, National Heart and Lung Institute
Dr. Sadek Hilal, Neurological Institute, Columbia-Presbyterian Hospital, N.Y.

COOPERATING UNITS (if any)

Neurological Institute, Columbia-Presbyterian Hospital, N.Y.
National Heart, Lung, and Blood Institute

LAB/BRANCH

Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION

DCRT/NIH

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.55	.50	0.05

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

PEEP/DECIDE/GRAPH is an interactive programming system written in SAIL, the Stanford Artificial Intelligence Language, and operating on the DCRT PDP-10 computer. PEEP is designed for picture processing applications, DECIDE is intended for algorithmic decision making and exploratory data analysis, and GRAPH has capabilities for two and three dimensional graphics. The system was originally written for the NCI Bladder Cancer Image Processing Project but is of wide utility. We will continue to make PEEP/DECIDE/GRAPH available for public use.

PHS-6040
(Rev. 10-76)

In the PEEP system and appendages to it, objects can be obtained from optical density histograms using several approaches. This option is available in global and local form. Derivatives, Laplacians, Hueckel and other edge detection operators can also be applied. A large library of feature extraction algorithms has been built.

These features encompass numeric descriptions of size, shape, content, contrast, comparison, texture and orientation. Examples of such features are area, average brightness, diameter, average chord, entropy, kurtosis and skewness of the optical density histogram, integrated optical density, variation in brightness, variation in chord length, variation in diameter, Fourier coefficients of a boundary, bending energy, medial axis transforms, major axis and minor axis.

DECIDE enables the performance of parametric and non-parametric recognition of objects. Linear and quadratic discriminant analysis form the basis for parametric recognition. Coefficients of the best discriminant function can be learned from exemplary objects using a learn command. New test objects can be classified into a learned category using the classify command. The user has control over various parameters of the learning process. For example, likelihood maximizing discriminant functions can be developed. Non-parametric recognition is performed by the cluster command. Again, many variations of data normalization, cluster merger strategy and cluster type emphasis are available.

GRAPH allows the user to create and display graphic structures in two and three dimensions and to use different vantage point for viewing them.

1978 Activities

The three subsystems were merged into one and PEEP data formats were changed to be compatible with MLAB. In addition, the Fourier analysis of curves and GRAPH have been incorporated into MLAB.

In collaboration with Dr. K. Kent at the National Heart, Lung and Blood Institute, a project was continued in order to make use of the decision making capabilities of DECIDE. An on-line expandable data retrieval system had been designed for the purpose of compiling data on the natural history of patients with coronary artery disease. Data on 200 to 300 patients over a period of two years will be collected and entered by means of a special questionnaire. A general purpose input program STOW for composing questionnaires leading to data structures compatable with DECIDE has been written and tested. Decision making logic will be developed so that a prospective diagnostic scheme can be obtained. From time to time graphic display is necessary. This project is similar but more elaborate than another National Heart, Lung and Blood Institute collaborative program designed to study pre and post-operative factors indicative of surgical risk.

In collaboration with Dr. Sadek Hilal of the Neurological Institute, Columbia-Presbyterian Hospital, New York, PEEP was used to apply automated pattern recognition to EMI computed tomography scans of the human brain. A computer decision tree method was devised to extract tumorous and edemous regions in the brain scans. We are awaiting receipt of a data tape containing 20 sets of brain scans with different types of tumors for analysis. It is anticipated that the new texture measures in PEEP will be diagnostic.

Future Plans

The PEEP/DECIDE/GRAPH interactive programming system is very large, when loaded in PDP-10 core it occupies 100,000 words. The system will be maintained in its present form for public use. A conservative policy will be maintained with respect to adding new image processing algorithms to PEEP because of its size. New routines will be maintained in parallel with PEEP.

The collaboration with the Neurological Institute will containue. New boundary definition procedures will be applied to organ location and tumor localization. New texture measures will be tested to see if they correlated with tumor type.

Little activity is expected on the NHLBI project.

Publications

Wu, S.C. and Prewitt, J.M.S.
Deriving Concavities from the Fourier Coefficients and Its Role in Pattern Recognition. Proceedings of the 30th Annual Conference on Engineering in Medicine and Biology, 1977.

Wu, S.C., Prewitt, J.M.S. and Lehman, J.
To Extract a Connected Object of Arbitrary Shape from its Background by Decision Tree Method. IEEE Computer Society Conference on Pattern Recognition and Image Processing. Chicago, Ill. June, 1978,pp.352-353.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT 00029-03 OSTC/OD

PERIOD COVERED
October 1, 1977 - September 30, 1978

TITLE OF PROJECT (80 characters or less)

Bladder Cancer Image Processing

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Judith M.S. Prewitt, Ph.D.

S. C. Wu, Ph.D.

Gilbert H. Friedell, M.S., Chief of Pathology, St. Vincent Hospital

Enrique A. Soto, M.D., St. Vincent Hospital

COOPERATING UNITS (if any)

Pathology Department, St. Vincent Hospital, Worcester, Mass.

Image Processing Laboratory, Jet Propulsion Laboratory, Pasadena, Calif.

LAB/BRANCH
Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION
DCRT/NIH

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.00	.95	0.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Summary

This project involves the application of digital computer technology to the diagnosis of disease based on the microscopic morphology of stained tissue sections. Techniques of digital image processing are applied to delineate nuclei in digital images of human urinary bladder epithelium and to compute mathematical characterizations of various morphologic attributes such as size, shape, texture and tissue architecture. Techniques of statistical decision theory and cluster analysis are applied to the problem of objectively characterizing tissue sections and devising classification and grading systems for them based exclusively on quantitative morphometry and biochemical composition.

PHS-6040
(Rev. 10-76)

Objectives

The long range goal of this project is to quantitatively characterize the epithelium of human urinary bladder from scanned digitized images of stained sections using digital computers and to develop a data-directed taxonomy for the range of tissues from normal to invasive carcinoma.

1978 Results

This project, inactive for a while, was reactivated with the change in programming staff in FY77.

The data base was not altered and consisted of images of tissue sections. Tissue sections were prepared on microscopic slides at St. Vincent Hospital, Worcester, Mass. and stained with hematoxylin. They were scanned at the Jet Propulsion Laboratory, Pasadena, Calif. so that the resulting images were at 630X, sampled at half micron intervals and rendered in 256 linear gray levels. The material was routine clinical preparations of variable and sometimes mediocre quality. The absorption peak for the tissue sections was determined to be at 570NM and all scans were made at both this wave length and in white light. In one experiment with tissue sections stained with gallocyanin chromalum, the response in the entire visible range was assessed.

The PEEP/DECIDE/GRAPH system was used to analyze the digitized images. (In fact, the project was the impetus for implementing that system, which is discussed in a separate project report). All of the object extraction methods were applied to digitized images of tissue sections. They met with varying degrees of success and depending on the quality of the tissue sections, one or another method may be necessary.

Two morphologically distinct tissue sections were chosen for in-depth study. Both yielded to thresholding for obtaining nuclear images. The entire armamentarium of PEEP features was extracted on approximately 20 nuclei from each tissue. Linear and quadratic discriminant analysis and cluster analysis were used to learn each tissue section as a category. Specimens from each tissue were then classified with the following result of demonstrated internal consistency: nuclei in one tissue type were overwhelmingly more like each other than like cell nuclei from other tissue types.

A new algorithm for shape assessment, based on a complex number representation of arc length along a boundary, was developed. All concavities can be found and the area between each one and the subject curve measured. In addition, the orientation of the object under study can be obtained from the Fourier coefficients. The technique was applied to blood cells and bladder epithelium nuclei for test purposes.

A new method of boundary following by using several threshold values within a range of gray levels iteratively and optimizing a function has been developed and successfully applied to finding the boundaries of nuclei. The starting threshold is the point of reflection of the left half of the optical density histogram to the first mode with an upper limit being set to the range of optical densities for the dynamic search. At each threshold the area is calculated and a linear function of two boundary features taken at successive threshold. The maximum of this function over all

thresholds is chosen as the threshold to find the boundary.

The two morphologically distinct tissue sections also were subjected to a new decision tree method to separate the nuclei from background since many nuclei have some internal pixels with lower gray level than at the boundary. Using 20 nuclei in each tissue quadratic discrimination using the features nuclear area, nuclear density, nuclear absorbance, standard deviation of nuclear density, entropy of nuclear density, and three texture measures, 100% correct classification of nuclei as coming from the parent tissue was obtained. A cluster analysis using the same features had a 6% error rate.

Significance

The data directed classification of tissue sections might well be an improvement over current subjective and often dubious decisions. The difficulty of the undertaking should not be under emphasized. Classification using algorithms may lead to greater objectivity, public verifiability, and greater consistency. There is always the opportunity for discovering new significant differences in optical properties between papillomas and papillary carcinomas using the digital computer.

Future Plans

At the present time, the project has been reactivated and will remain so, especially if suitable tissue section material becomes available. The same techniques will be applied to cervical biopsies paired with cytology which will be obtained from the University Hospital, Uppsala, Sweden.

Publications

Prewitt, J.M.S., Barber, A. and Wu, S.C.
An Application of Pattern Recognition to Histology. IEEE Computer Society Conference on Pattern Recognition and Image Processing. Chicago, Ill. June 1978. pp. 499-506.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do **NOT** use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 CT 00028-03 OSTC/01

PERIOD COVERED
October 1, 1977 - September 30, 1978

TITLE OF PROJECT (80 characters or less)

Characterization of Cells from Breast Aspirates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Judith M.S. Prewitt, Ph.D.
Bjorn Stenkvist, M.D., University Hospital, Uppsala
Jan Holmquist, Ph.D., University Hospital, Uppsala

COOPERATING UNITS (if any)
Department of Clinical Cytology
University Hospital, Uppsala, Sweden

LAB/BRANCH
Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION
DCRT/NIH

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.00	2.00	0.00

CHECK APPROPRIATE BOX(ES)

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Summary
This project involves the application of digital computer technology to the diagnosis of disease based on microscopic morphology of cell specimens. Techniques of digital image processing are applied to delineate objects of interest in digital images of human breast aspirates and to compute mathematical characterizations of various morphologic attributes such as size, shape and texture. Techniques of statistical decision theory and cluster analysis are applied to the problems of classifying or identifying individual cells and defining a grading system for smears.

PHS-6040
(Rev. 10-76)

The objectives of this project is to characterize images of cells from human breast aspiration biopsies, and to distinguish malignant from benign cells. Aspiration biopsy is used widely in Europe but not in the United States.

Biopsy material was prepared at the Department of Clinical Cytology, University Hospital, Uppsala Sweden, stained with Papanicolau stain and scanned there, digitized and recorded on magnetic tape. The Uppsala scanning microscope formerly had 7/10 micron square aperture and had a moving stage and recorded 256 gray levels. The current model uses a 256 element linear photodiode array. Using the PEEP system, cell images were displayed and thresholded. This generated objects which were subjected to feature extraction using the PEEP/DECIDE system. Eighteen numeric characterizing features were extracted for each of 100 cell nuclei in five cell categories. Examples of these features are area, average brightness, average chord, entropy, kurtosis and skewness of the optical density histogram, density, variation in brightness, variation in chord length and variation in diameter.

Each of four categories of benign cells was distinguished from the category of malignant cells. Using quadratic discriminations, combinations of as few as four features and in many cases a single feature allowed perfect discrimination between pairs of cell categories. Useful features included skewness of the optical density histogram, nuclear area, length of major axis, density and entropy.

A manuscript, "Computer Assisted Identification of Cells in Needle Aspirates of Mammary Tumors", has been presented at MEDINFO'77 and published in the Proceedings.

Significance

The practical significance of this research lies largely in developments in the automation of cytologic examinations and in the quantitative, objective investigation of the correlation of microscopic morphology with the prognosis of disease. The project will be continued both in the United States and Sweden using more carefully scanned cells prepared with gallocyanin chromalum.

Future Plans

We are awaiting the arrival of data tapes from Sweden containing 10,000 digitized images of breast tumor cells stained with gallocyanin chrome alum and scanned with a new linear photodiode array scanner at 0.5μ for analysis. We are also awaiting the arrival of data on the relative grading of 100 smears for purposes of analysis by multidimensional scaling. In addition, we plan to use cluster analysis to detect patterns or trends in epidemiological data accompanying the cell images.

Project Description, Objectives and Significance

The field of image processing in medicine is in a state of rapid flux as a result of new techniques such as computerized tomography and ultrasonography. These consulting activities are necessary to help take my experience and expertise gained in the mathematics and computer programming of image processing to other groups and to bring back information about progress in areas outside of DCRT.

Activities in 1978

- .member of the Board of Directors of the Biomedical Engineering Society and Associate Editor of Computer Graphics and Image Processing,
- .reviewer IEEE Transactions, Computer Programs in Biomedicine, Computer Graphics and Image Processing,
- .steering committee of the Dahlem Conference on Biomedical Pattern Recognition,
- .organizer, Short Course on an Introduction to Biomedical Image Processing for October 1978 ACEMB meeting,
- .membership in the NSF Inter-Agency Panel on Medical Physics, the NSF Automation Research Council, and chairmanship of the NSF Committee on an Ultrasonic Tissue Signiture Library.
- .work on the IEEE Pattern Recognition and Machine Intelligence Group and its subcommittees on Image Processing and Scene Analysis, Data Bases and Biomedical Pattern Recognition,
- .steering committee and treasurer 1979 IEEE Computer Society Conference on Image Processing in Radiology,
- .organizer, session on Computerized Tomography, 1978 IEEE Conference on Pattern Recognition and Image Processing,
- .the Division of Cancer Biology and Diagnosis of the National Cancer Institute as a member of the Diagnostic Research Advisory Committee,
- .the National Heart, Blood and Lung Institute, Division of Research Resources, RANN, The Division of Computer Research and the Division of Engineering of the National Science Foundation,
- .consultant NCI/DCBD Computerized Transaxial Tomography Project,
- .ad hoc reviewer NCI/DCBD Dose Reduction in Computerized Tomography project,
- .NCI representative to Standard Protocol for Evaluation of Imaging Techniques in Cancer Diagnosis project,
- .faculty DCRT Computers in Clinical Medicine Elective.
- . a National Visiting Lecturer for the Society for Industrial and Applied Mathematics (SIAM) on topics related to image processing and decision analysis and Visiting Lecturer and Scientist, Department of Computer Science and Numerical Analysis and Department of Clinical Cytology, University of Uppsala, Uppsala, Sweden.

Future Plans

It is anticipated that the same level of consulting activites will be maintained in fiscal 1979 with the same federal agencies, and profes-

sional societies receiving advice and assistance. In addition, I will be on the advisory board of the new IEEE Transactions on Pattern Analysis and Machine Intelligence.

Publications

Prewitt, J.M.S.
On Some Applications of Pattern Recognition and Image Processing to Cytology, Cytogenetics and Histology. Doctoral Dissertation, Department of Computer Science, Uppsala University and Department of Clinical Cytology, University Hospital, Uppsala, Sweden, April 1978.

Prewitt, J.M.S.
Reconstruction Software for Computerized Tomography. Proceedings of Computer Software Applications Conference 1977, IEEE Press, 1977, pp. 285-292.

Prewitt, J.M.S.
Interactive Decision-making for Picture Processing. Proceedings of the 1977 IEEE Conference on Decision and Control, IEEE Press, 1977 pp. 373-379.

Prewitt, J.M.S. and Mendelsohn, M.L.
Analysis of Cell Images. Reprinted in Machine Recognition of Patterns, ed. by A.K. Agrawala. Wiley, New York, 1977, pp. 362-380.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00038-01 OSTC/OD

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Natural Language Access to Clinical Data Bases

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Martin N. Epstein, M.S., Research Programmer, DCRT

COOPERATING UNITS (if any)
SRI International, Menlo Park, California
University of California, San Francisco, California

LAB/BRANCH Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION
Division of Computer Research and Technology

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.9	.9	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this research is the development and evaluation of a system, called MEDINQUIRY, that will allow physicians personal access to patient medical data through natural language queries to support both patient management and clinical research.

A prototype MEDINQUIRY system has been implemented for a small data base on malignant melanoma. The physician can input queries in English that retrieve specified data for particular patients or for groups of patients satisfying certain characteristics, that perform simple calculations, that allow browsing through the data base, and that assist in identifying relationships among attributes.

Objectives:

1. Develop a clinical data base system that will allow clinicians personal access to data on specific diseases using queries formulated in English.

2. Collect and maintain in machine readable form clinical and histological data on patients with malignant melanoma and cancer of the colon for use in the system.

3. Study the use of the system by physicians.

4. Evaluate the effects of using the system to aid the physician in patient management and in studying the clinical course of the disease more precisely.

Methods:

A system called "LIFER", developed at SRI International, provides a facility that allows a language interface builder (in this case the PI) to specify rules required to process English language query requests. These rules are used to create and modify the grammar, lexicon, and language interface functions. These tasks can be accomplished on-line and is one of the major attractions of the approach pursued. Special purpose facilities available include an ellipsis capability to process incomplete data, a spelling corrector, and a paraphrase mechanism for relatively unsophisticated users to add new rules to the system. A requestor can follow a line of inquiry to test a particular hypothesis by entering a sequence of requests that depend on each other.

Findings:

1. The methods applied provide a stepwise facility for determining the classes of questions that physicians desire to ask of a clinical data base.

2. Through use of the English language access facility, hypotheses on melanoma that have been established in the literature can be confirmed and new hypotheses can be tested.

3. The availability to physicians of on-line English language access has encouraged a more active interest and participation by physicians in the data acquisition process, in completing missing values in the data base, and in actively pursuing the information in the data base.

4. MEDINQUIRY has been demonstrated to physicians who are specialists in melanoma, other cancers, and a variety of other diseases. The reactions have been uniformly positive, even though the existing data base is not large enough to provide significant results. The ability to formulate queries in ordinary English and to have the results displayed immediately is extremely appealing. The facility for correcting spelling errors received special commendation.

5. As originally collected, the melanoma data base was incomplete and contained many errors. An extensive effort was required to extract the data elements from the primary records, to edit the attributes and values, and then to create the data base.

Proposed Course:

1. Extend the capabilities of MEDINQUIRY as an experimental system with an expanded data base on melanoma.

2. Create a second data base for Cancer of the Colon to test the generality of the concepts developed for melanoma data access.

3. Incorporate a knowledge base in the system to reflect physician defined higher order concepts and thus reflect the current state of medical understanding of the disease. A knowledge base also would contain rules for understanding the context of requests and developing appropriate prompts and paraphrase capabilities that show a greater degree of understanding of the medical domain.

4. Evaluate the use of the system by physicians and study the requirements for adapting the system for different diseases and on other computer systems.

Potential Significance to Biomedical Research:

1. Aid the physician in clinical practice in planning therapy and assessing prognosis for his/her patients.

2. Assist the clinical investigator in identifying and studying the relationships among data attributes.

3. Study the potential applications of such systems in the conduct of clinical trials. In particular, they may be used to assess the efficacy of therapeutic protocols.

4. Provide convenient access to medical data bases to allow physicians to browse through their data and more adequately study the clinical course of a disease.

Publications:

Epstein, M.N., and Kaplan, E.B.: Criteria for Clinical Decision Making. In Schneider, W. and Sagvall-Hein, A.L. (eds.): Computational Linguistics in Medicine. North-Holland Pub. Co., 1977, pp. 35-44.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00032-02 OSTC/OD

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Tumor Growth Curves

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

Judith M.S. Prewitt, Ph.D.

COOPERATING UNITS (if any)

LAB/BRANCH
Office of Scientific and Technical Communication

SECTION

INSTITUTE AND LOCATION
DCRT/NIH

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.05	.05	0.00

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A manuscript on tumor growth curves is being revised. A new second order non-linear differential equation for monotonic growth is proposed. This equation contains all classic models such as the Gompertz, logistic and exponential as special cases, and introduces an infinity of intermediate curves with varying inflection points. The solutions to the growth equation are obtained in closed form, and can be expressed in a time-free form which allows inter-comparison of the shape of different growth curves independent of age and dependent only on tumor extent. Numerical solution of equations to fit the general growth curve to data is unique. This equation should facilitate comparing data from different laboratories and provide an intrinsic characterization of the growth phenomena.

PHS-6040
(Rev. 10-76)

July 1, 1977 through June 30, 1978

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT

2. OFFICE OF ADP POLICY COORDINATION

3. Henry J. Juenemann
Chief

I. SUMMARY

Function

The Office of ADP Policy Coordination, under the direction of the Assistant Director of the Division, has two closely related function. It serves as:

- a focus for NIH-wide coordination of automatic data processing policy matters.

- a central NIH point of contact with the Public Health Service, the Department of Health, Education and Welfare, and other HEW agencies, the General Services Administration and the Office of Management and Budget on policy questions and NIH's participation in policy development.

Scope

The Office provides advice and assistance about internal DCRT operations and coordinates DCRT's ADP policies and activities with those of other agencies. This includes advising the Director of DCRT and through him the Director of NIH on ADP policy matters, assisting the NIH Division of Management Policy on questions relating to its responsibility for administrative computer applications, reviewing and evaluating proposals from NIH B/I/D/O's for ADP and computing procurements and contracts, directing the development of the annual NIH ADP Plan, representing the NIH in PHS and DHEW policy formulation efforts, working with GSA and OMB staff on procurements, coordinating Interagency Agreements with other Federal agencies that use DCRT facilities, and answering inquiries from scientists and administrators who are confused by the whole process.

Highlights of the Year's Activities

The annual ADP Plan, required by DHEW was again completed. This management process, involving all B/I/D/O provides a forward look at projected ADP efforts necessary to support NIH research and research management programs. It showed a 53 million dollar, 654 man-year ADP program in place during Fiscal Year 1978 growing to 58 million dollar and 676 man-years by Fiscal Year 1979.

One major accomplishment of the office during the year was the development of an easy to use set of instructions for NIH staff offices to use when

ordering teleprocessing services from the private sector. GSA had established a mandatory program for this but the GSA instructions contained ambiguities and were not easy to use in the NIH environment. Therefore, in conjunction with Procurement Branch, a set of instructions specifically tailored to NIH needs were developed to ease the burden on NIH.

In the process of monitoring the policy implications of NIH's ADP involvements and assuring conformity to existing OMB, GSA and Department regulations, this office reviewed 300 proposals for ADP equipment or services during the period. This is a 70% increase over the corresponding period last year.

A total reprocurement of the IBM System 370 component of the DCRT/NIH central computing facility has been mandated by GSA. The strategy for the recompetition was largely worked out with GSA during the year. Extensive discussions with GSA and the Department finally resulted in GSA allowing a more reasonable approach than they had been willing to allow over the past few years. The solicitation document is now being prepared. Due to the complexities of the NIH central 370 utility, that effort will undoubtedly stretch well past the close of FY80 and will consume significant levels of highly skilled and scarce technical talent from the Division.

Later in the fiscal year, in spite of objections from the Division, the Office of the Secretary directed that two of the four central processing units in the central IBM 370 System, which are subject of the total reprocurement effort, be converted from lease to purchase.

Another total system reprocurement is simultaneously being conducted for the Division's scientific time sharing DECSystem 10.

The competitive solicitation for editing disply terminals to be available NIH-wide which GSA had approved last year was finally completed after more than two and half years delay caused by disagreements with GSA. Competitive solicitations for two other types of terminals were under way as the end of the year approached.

In reviewing proposals for contracts or in processing equipment acquisitions, this office is very fortunate in being able to call on the consultive expertise of the other laboratories and branches of DCRT. During the year they were extremely helpful in insuring technical merit is part of the review process.

Future Plans

Federal ADP policies and requirements continue to become more and more complex as OMB, GSA, DHEW and PHS become more and more involved. As a result, the office must spend an increasing portion of its available man-hours in attempting to guide NIH policy in productive directions and in meeting regulatory requirements. The office will continue to work to spare large numbers of NIH research and research support staff members the task of becoming expert in the many nuances of ADP-related regulations. However, it is anticipated that the two simultaneous full recompetition efforts for

both of NIH's main computer systems will consume most of the resources of this office during the upcoming year and will in addition, require extensive assistance from OD and CCB staff.

October 1, 1977 through September 30, 1978

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

1. DCRT

2. OFFICE OF ADMINISTRATIVE MANAGEMENT

3. L. Lee Manuel
Chief

I. SUMMARY

Function

The Office of Administrative Management, under the direction of the Executive Officer, provides administrative, financial and personnel functions to support the Division's programs. The office serves as liaison to these functions with the NIH Office of Administration and other OD, NIH offices.

Scope of Activities

The office handles the usual range of administrative managerial functions for an NIH research division of almost 300 people. The Financial Management/Project Control Sections are currently tracking 2000 project accounts involving 6000 registered users of the DCRT computer facilities and services. These services have grown to an estimated $30,000,000 in FY 78. Requisitions, contracts, travel, and training documents are processed by the Administrative Services Section and covers a variety of procurements of approximately $20 million.

Highlights of Years Activities

The Personnel Section, in compliance with Civil Service Commission and DHEW directives, continued the position-classification review of all positions. Also the conversion of position descriptions to the new Factor Evaluation System began to be implemented.

Major space and renovation continued for Building 12 and 12A. The Administrative Services Section implemented new procedures in the areas of payroll processing, check distribution, and procurement documents. It also did a major review of DCRT staff identification codes for the revised NIH mailing key system for document distribution. DHEW initiatives in the areas of grants, contracts and consulting services required the preparation of numerous detailed recurring reports and plans for the current fiscal year and will continue into FY 1979.

Future Plans

The coming year will include major moves and other renovations within Buildings 12, 12A and 12B. These will allow consolidation of some currently scattered DCRT staff and more unified services for DCRT clients. There will, undoubtedly, be new administrative managerial requirements and modifications of old ones forthcoming from the NIH, the PHS, the Department, the GSA and the Civil Service Commission. These requirements will be implemented within the framework of DCRT program policy.

Oct. 1, 1977 through Sept. 30, 1978

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT

2. LABORATORY OF STATISTICAL AND MATHEMATICAL METHODOLOGY

3. James E. Mosimann
Chief

I. SUMMARY

Function

The Laboratory of Statistical and Mathematical Methodolgy (LSM) combines research in mathematical statistics, mathematics, computer and information science, with collaboration and service in these areas to NIH researchers and administrators. There are four sections in LSM:

- The Statistical Software Section (SSS) provides consultation to and collaboration with NIH researchers and administrators in all computational aspects of biomedical data analysis, including selection and support of large program packages. Three specialists in scientific programming are led by a computer systems analyst whose specialty is statistics.

- The Biomathematics and Computer Science Section (BCS), directed by a mathematician, performs independent research and provides consultation and collaboration in the specialties of its eight mathematicians, computer scientists and programming aides.

- The Statistical Methodology Section (SMS) works closely with the Statistical Software Section. Four individuals who work under the direction of a mathematical statistician provide biostatistical consultation and do independent research.

- The Medical Information Science Section (MIS) investigates and develops methods for application of information and computer science to medical language data processing. Five individuals work under the direction of a computer systems analyst who specializes in computational linguistics.

Scope of Work

LSM staff interact with all NIH institutes and with government

agencies outside HEW. Fiscal year 78 was LSM's fourth year as a separate entity within DCRT. The volume of its computational and consultation services continued to expand while its research activities were maintained at about the same level as the preceding year.

Highlights of the Year's Activities

Computation. A major part of LSM activity is the offering of statistical and mathematical program packages to the NIH user community. LSM accepts responsibility for evaluation of new program packages and their suitability for NIH. When LSM does offer a package to the NIH community, LSM makes three basic commitments:

- The maintenance of the package, with adequate documentation, through NIH computer system changes, package updates and corrections.

- The rapid response to queries concerning user access to a package program including job control language and program parameters.

- The assistance in interpretation of results.

During this year, as in the past year, SSS maintained the following program packages and programs:

BMD, Biomedical Computer Programs, UCLA
BMDP, Biomedical Computer Programs, P-series, UCLA
SPSS, Statistical Package for the Social Sciences, SPSS, Inc.
SAS, Statistical Analysis System, SAS Institute, Inc.
PSTAT, Princeton Statistical Package, Princeton University
IMSL, International Mathematical and Statistical Libraries, IMSL Inc.
MSTAT1, Collection of Mathematical and and Statistical Programs, DCRT.

The effort expended in the commitment to maintain these packages is considerable. During this year every package went through at least one update. The effort expended in response to queries concerning package access is also considerable and requires continuous availability. During the year over 4,000 calls were responded to by SSS staff alone. Two courses were taught on each of the packages SPSS, SAS, and one on BMDP.

The use of program packages has shown considerable increase this year over fiscal 77. The average accesses per month of all the statistical packages rose from 6000 during fiscal 77 to almost

9000 in fiscal 78. For the second year in a row SAS experienced the largest increase of any of the packages. SAS averages almost 4000 accesses per month, up from 2000 per month in fiscal 77. The average number of accesses per month for SPSS increased from 2600 to 3900, an increase of 50% over the last year for SPSS. The average combined accesses of the BMDP and BMD packages decreased from 900 accesses per month in fiscal 77 to around 750 accesses per month this year. BMDP was up slightly from 600 average accesses per month in fiscal 77 to 650 average accesses per month this year, while BMD went down from 360 average per month to 100 average accesses per month in the same period of time. As an example of a package used for specialized purposes, PSTAT averaged 20 accesses per month, down from 30 average accesses per month in fiscal 77. The main programs in MSTAT1 averaged 150 accesses per month, which is about the same as in fiscal 77. The subroutine usage of MSTAT1, which can only be estimated, is much higher than the main program usage. Accesses to the IMSL package cannot be counted, but it is estimated that usage increased during fiscal 78.

The Biomathematics and Computer Science Section maintains two computer packages for biomathematical modeling at NIH: MLAB on the PDP-10 and MODELAIDE on the S/370. Both packages were developed by BCS staff members. MLAB is widely used at NIH and in many other locations in the U.S. and abroad. It has been used by hundreds of NIH biomedical researchers, with only occasional contacts with BCS computer specialists needed in most cases. MODELAIDE is not so widely used, but has greater capabilities than MLAB for analysis of very large models. During the fiscal year, MLAB was improved by addition of new curve-fitting control strategies, and addition of hidden-line suppression to the three-dimensional graphics facilities. A new reference manual for MLAB was distributed near the end of last fiscal year, and the next edition of the reference manual is now in preparation. A beginner's guide to MLAB is in preparation, with distribution expected within a few months. An introductory course for MLAB was taught twice during the fiscal year. A number of new features are currently under development for MLAB, including contour map graphics and fast Fourier transform capability.

BCS continues support of C-LAB, a computer package for pattern recognition and cluster analysis developed by a BCS staff member. A number of new analysis algorithms have been added, and existing methods improved. C-LAB compatibility with MLAB has been maintained. A course in C-LAB was taught during the fiscal year. Revision of C-LAB documentation is now in progress.

BCS also supports the University of Utah computer package REDUCE, for symbolic manipulation of algebraic and differential equation

formulas.

BCS staff members also taught courses in the SAIL programming language and in curve-fitting methods.

Consultation. The diverse nature of LSM consulting is indicated by the projects and activities listed in Part II. This list is a sample of activities and is not exhaustive.

The pattern of LSM consultation activity remained similar to that observed in the previous fiscal year. Estimated percentages during fiscal 78 are shown below:

. Mathematical or statistical advice with limited computer use	10%
. Mathematical or statistical advice with considerable computer use	50%
. Computational advice alone	40%

The continued availability and use of general-purpose statistical and mathematical packages like SAS and MLAB has maintained the large component of computer use in these figures. MIS activities, which involve relatively little consultation, are not represented in the above percentages.

As in previous years there was considerable variation in the amount of time required for an LSM consultation. Some very brief consultations are very successful, and are brief precisely because there is a known answer to the statistical/mathematical question posed. Other consultations involve extensive time and statistical/mathematical research as well. For example, the collaboration over the past three years with Dr. A. Cheever, Laboratory of Parasitic Diseases, NIAID, on the study of schistosomiasis continues actively. This consultation has provided an excellent data base for application of size and shape statistical methods developed by the Chief and staff of LSM. Several publications resulting from this collaboration are now published or in press.

Many consultations which involve considerable LSM effort do not involve new statistical research. For example, LSM provided many computer statistical analyses for studies of atherosclerosis conducted by Dr. William Roberts, NHLBI, during fiscal 78. The data base consists of autopsy and other information from deceased atherosclerotic patients, including measurement of major coronary vessel narrowing, Calcium, Iron, hemorrhage, thrombus, constituents of plaque, medical history, demographic information, and so on. Some studies compared vessel pathology within or between certain groups of patients, either comparing diseased with control groups or comparing groups with different forms of

heart disease. Other analyses consider patterns of pathology within individual patients, such as comparison of Calcium with heart valve damage, comparisons of narrowing of different vessels or at different points on the same vessel, comparison of vessel pathology with vessel size or heart size, and so on. Studies were also made involving demographic factors such as sex and age. Many analyses were straightforward statistically, but required care and attention to detail in problem formulation and computer analysis.

Research. BCS research included projects in biomathematics, general mathematical methods, and computer science. Research continued on the "symmetric axis" method of shape description, including substantial improvements in computer algorithms for general-purpose symmetric analysis for shapes. A cooperative study of human mandible growth and development using symmetric axis methods is in progress. The principle investigator recently visited France, lecturing on visual and geometric theories by invitation of Professor Rene Thom.

Cooperative effort continued on a project to develop a cancer diagnostic tool using data from a fluorescence-activated cell-sorter. A new curve-fitting algorithm for stiff differential equation models was developed, facilitating computer analysis of larger models. A formal logic appropriate to several varieties of algebra used in applied mathematics was developed. Research on computer storage and retrieval algorithms is continuing.

In SMS, research on multivariate statistical methods has been active during this fiscal year. Research on size and shape methods has drawn interest from the statistical community, with Prof. G. P. Patil of Pennsylvania State University, Dr. Ian James from C.S.I.R.O., Melbourne, Australia, and Dr. John C. Gower, Rothamsted Experimental Station, England, visiting LSM for research discussions during the fiscal year. These methods have been improved and tested on various biological and medical data bases during fiscal 78. A study of procedures for multiple ratio estimation was undertaken, with application to a one-factor allometry model.

The Medical Information Science Section system for information storage and retrieval of pathology was reviewed for application to autopsy reports. Further improvements were made in the formal rules for automated morphosemantic segmentation of medical compound words derived from Greek and Latin, and for paraphrasing them in English and French medical languages. Work continued towards the development of a formal and practical basis for the construction of computer-oriented medical microglossaries.

Future Plans

No major shift in laboratory service or research is anticipated in the coming year. Current levels of support of statistical and mathematical program packages, and consultation and user assistance will be maintained or expanded. Biomathematical and biostatistical research projects will be continuations of those already initiated and reported here.

II. LSM PROJECTS AND ACTIVITIES

The following list contains major LSM consulting activities of the year. Following the list of publications, the LSM individual research reports are presented.

Prenatal bone development in rhesus monkeys. M. Michejda, VR, DRS. Surgical examination of rhesus monkey fetuses was conducted at several fixed post-conception time intervals and at birth, with wrist-bone ossification examined in each case. LSM designed a statistical model using Markov processes for analysis of the data, and computed numerical results based on the model.

Nurse job satisfaction evaluation. R. Carlsen, NURS, CC. This study was developed to describe the level of job satisfaction of primary vs. team nursing. LSM assisted in the design of questionaires and in contingency table analysis of question response data. LSM has collaborated on this project for more than one year, and a joint publication is in preparation.

Behavior of coati. H. Smith, LDN, NICHHD. Ethograms were constructed representing the behavior of coati (raccoon-like carnivores) in captivity and in the wild. LSM assisted in data arrangement and editing, and in analysis of data by two-way ANOVA and multiple regression.

Atherosclerosis pathology studies. W. Roberts, IR, PA, NHLBI. Data obtained from autopsies and medical histories of deceased atherosclerotic patients was analysed for the effects of many different factors. LSM provided continuing statistical advice and computer analyses, primarily using SAS, for evaluation of different aspects of the data.

Hemoglobin kinetics. R. Berger, B. Balko, P. Smith, TD, NHLBI. LSM assisted in developing suitable methods for curve-fitting and solving differential equations for simulation of hemoglobin-ligand binding, and experimental control on a laboratory minicomputer.

Redox studies of Cytochrome. R. W. Hendler, LB, NHLBI. One experiment consists of about 50 spectra. Each spectrum, at a distinct voltage, has small sharp peaks superimposed on broad background peaks. LSM assisted in developing methods to separate the small peaks from background and from each other, and to explain their growth with voltage in terms of cytochrome oxidation.

Oxygenation of whole blood. R. M. Winslow, CL, NHLBI. LSM provided consulting on curve-fitting technique, e.g. developing routines for approximating two-dimensional surfaces.

Fumarase kinetics. I. Darvey, PSL, DCRT, L. Kohn, LPB, NIAMDD. LSM offered advice on possible methods for distinguishing or deriving mechanisms to explain the suppression of enzyme activity at high substrate concentrations.

Copper kinetics in Man. E. A. Jones, J. M. Vierling, DD, NIAMDD and W. Rumble, R. Aamodt, NM, CC. A paper was published on uptake of copper by ceruloplasmin and its implications for the diagnosis of various copper overload diseases. Discussions have been held about possible expanded study.

Scintillation counting. Ramon Tate, CSL, DCRT, Joe Fenstermacher, CHPH, NCI. Least generalized variance experimental design has been found efficient (in the vector minimization sense) in some cases, but there are counter-examples. LSM is assisting in evaluation of this measure's efficiency for scintillation counting experiments.

Pharmacokinetics. R. Lutz, R. Dedrick, BEI, DRS. Large systems of differential equations, simulating drug distribution, are fit to data. LSM advised on modeling and possible use of the Modelaide system, since the formulas are too unwieldy for MLAB.

Enzyme kinetics. E. Silbergeld, et.al., LP, NINCDS. The mechanics of specifying and using Clelands initial rate models in MLAB was discussed and illustrated at length with real data.

Measurement of kidney size. P. Bradley-Moore, NM, CC. By taking lateral X-rays of the kidneys in addition to the posterior view, a more accurate measurement of kidney size can be made. A formula was developed for combining the results of the two views and adjusting the standard kidney length measurement accordingly.

Improvement of a standard clustering technique. C. Edelbrock, LDP, NIMH. Stein's method is being applied to the centroid method of clustering to produce improved hierarchical clustering diagrams (dendrograms). The method uses based estimators of multivariate means and provides better predictive value in general.

Study of biochemical polymers. F. Howard, LMB, NIAMDD. Polymers of Cytosine and Inosine are generated in vitro under controlled conditions, and amount of product containing specified numbers of Cytosine molecules in successive primary sequence locations is measured. LSM provided a theoretical formula, suitable for computer evaluation, of the amount of product expected assuming random growth of the polymer in proportion to the supply of each base in the preparation.

Immune function of the spleen in mice. M. Geier, SM, NINCDS. Measurements of labelled antigen persisting in the spleen are

compared with generation of antibody in mice during a period of days after injection of the antigen. LSM assisted in mathematical modeling and in generation of graphical displays using MLAB.

Repetition of primary sequence triplets in proteins. H. Saroff, LBC, NIAMMD. LSM provided advice and analysis on combinatorial probabilities associated with repetition of short peptide chains occurring in primary sequences of natural proteins.

Water quality data at NIH animal care facility. D. Wilson, ESS, DRS. Stream water quality parameters are monitored daily in Broad Run, above and below effluent emission from the Poolesville NIH animal care facility. LSM assisted in locating errors in MLAB procedures used to generate graphical displays of water quality data.

Sleep analysis. W. Duncan, AP, NIMH. The analysis focuses on examining the relationship between mental illness and sleep disorders. Discriminant analysis was employed to evaluate possible contribution of sleep variables in distinguishing between groups of normal subjects, depressed (unipolar and bipolar), and insomniacs patients.

Selection for body weight in mice. K. Smith, VR, DRS. The primary purpose of this project is to determine if a significant amount of genetic variation remains in highly inbred strains of mice. If it can be established that genetic variation does not exist in these strains, it should be possible to make changes in management procedures use to maintain these strains which would reduce the cost of production. The statistical programs developed in this study are directed toward providing an objective evaluation of the effects upon genetic variation in inbred strains of mice.

Kidney measurements. P.R. Bradley-Moore, NM, CC. Comparison of kidney contribution with hippuran and mercury was done with regressions and plots. Also, an empiric curve was derived to give the true length of angulated kidneys using projected length obtained from Camera Renography. Correlations were made of both the calculated true length and the projected length with IVP size.

NIH Library journals study. J.C. Boggess, L, DRR. All the requests for duplication of journal articles obtained in a three month period by the NIH Library were analysed with regard to year of publication, journal cost, multiple requests of articles, etc. Much file manipulation, using SAS, was needed to do various analyses. Frequencies, correlations, means were printed.

Organizational perceptions of secretaries and supervisors. W.E.

Mowczko, OAM, NIAMDD. Assistance was given in the development of the computer programs used to analyse the data in a comparison of the organizational perceptions of secretaries and supervisors in selected federal agencies.

Litigation data. M.P. Lockard, P, OD. A series of computer programs was written and executed, using personnel data, to obtain statistics needed by Justice Department lawyers to defend NIH personnel practices in a pending litigation. Statistical procedures used include regression and breakdown.

Triglyceride and HDL cholesterol: factors regulating HDL cholesterol levels. E. J. Schaefer IR MD, NHLBI. A database containing 1088 normal subjects and 856 hyperlipoproteinemic patients was submitted to LSM for statistical analysis. Several analyses of variance and intercorrelation analyses were performed. It was found that for both normal and hyperlipoproteinemic subjects, a negative correlation exists between HDL cholesterol and VLDL cholesterol and between HDL cholesterol and plasma triglyceride. HDL cholesterol levels were lowest in patients with fasting chylomicronemia and were decreased in hypertriglyceridemic subjects. As has been previously reported, females had significantly higher HDL cholesterol concentrations than did males. Age was not related to HDL cholesterol.

Norepinephrine production. C. Lake, I. Kopin, et.al., LCS, NIMH. Originally this study compared norepinephrine production in controls with that in several classes of hypertensives. Currently, the effects of drugs (pimozide, lithium, amphetamine, et.al.) on blood pressure, pulse, and norepinephrine-baseline as well as response to standing are under study. Subject types include normals, schizophrenics, cataleptics, manic depressives, narcoleptics, etc. The Statistical Analysis System (SAS) has been heavily used for data processing and statistical computing.

Quantitative analysis of interictal behavior in temporal lobe epilepsy. P. Fedio, CN, NINCDS and D. Bear, Harvard Univ. Patients with right or left temporal epileptic foci are contrasted with normal subjects and subjects with neuro-muscular disorders. Work continues on this project with periodic additions to the database and reanalyses. Discriminant analysis and analysis of variance are employed.

Microglossary for Dermatology. C. Brown, College of American Dermatologists. LSM assisted in evaluation of the SNODERM (Systematized Nomeoclature for Dermatology) microglossary, and consulted on its possible use for computer storage and retrieval of dermatology data.

English-German International Data Bank for Cancer. Institut fur

Dokumentation, Information und Statistic, Deutsches Krebsforschungszentrum, Heidelberg, West Germany. LSM consulted on development of a compatible encoder for English and German, intended as a tool available for creation of the proposed International Data Bank for Cancer.

Neural impulse modeling. J. Rinzel, MR, NIAMDD. Partial differential equations modeling propagation of neuronal impulses were obtained. LSM assisted in the preparation of three-dimensional graphical displays using MLAB.

Cancer screening analysis. J. Chen, FSS, NCI. Designing a cancer screening program involves selection of classes of people at risk to be screened. The biased sampling statistical analysis involved reguires numerical evaluation of several associated integrals. LSM assisted in computer evaluation using MLAB.

Standard curves for radioimmunoassay. A. Schrecker, LRMATV, NCI. Standard curves are required for assay evaluation, which can be obtained by curve-fitting normalization data. LSM assisted in curve-fitting a standard empirical formula and a model obtained from chemical kinetics, using MLAB.

Blood Measurements in Japan. E. Harris, LAS, DCRT. Daily measurements of red blood counts, albumin, and cholesterol concentrations were collected from 44,826 individuals in Japan during the period of December 1, 1970 to June 30,1977. Models to forecast future observations were derived by using Box-Jenkins time series techniques. The appearance of the autocorrelation and partial autocorrelation functions using different models as well as the Box-Jenkins goodness-of-fit significance test were used as guides in the selection of the simplest model.

Time Series of Creatinine Clearance Determinations. J. Klippel, A&R, NIAMDD. Along with LAS, DCRT, a series of creatinine determinations in twelve patients were studied to determine the possible effects of immunosuppressive drugs on renal functions in women with lupus nephritis. A cusum technique was used to detect step changes in the time series.

Induction of Rat Mammary Tumors. R. Evarts, CMT, NCI. The effect of hydroxylamine (HA) on the induction of mammary tumors in rats was studied. HA administration was started at age 36 days for one group of rats and at age 64 days for a second group; no HA was administered to a third group which served as a control. The statistical analysis consisted of the estimation and comparison of median latency periods by biological assay methods, the comparison of tumor incidences by Fishers's exact test for analyzing 2 x 2 contingency tables, and the comparison of the average numbers of tumors and average weights of tumors in tumor bearing animals by either Student's t-test or Satterwaite's approximation to the t-test.

Diazepam Assay. P. Skolnick, LC, NIAMDD. The percent inhibition of diazepam binding was determined at various concentrations of a drug. Biological assay methods were used to derive a standard curve from which dose concentrations were estimated for unknown curves.

Monkey Diet Fiber Study. M. Morin, VRB, DRS. Rhesus monkeys were randomly divided into four groups of 72 animals each. Three groups were fed experimental diets or 3%, 6%, and 9% crude fiber content respectively while the fourth group was fed a regular Purina diet of 3% crude fiber content. Comparisons of the mean gains in body weights, the mean number of treatment days for all monkeys, the mean number of treatment days for monkeys with diarrhea, and the morbidity of diarrhea were made for rats fed the four different diets. Statistical methods used in the analysis included Student's t-test, Satterwaite's approximation to the t-test, and Fisher's exact test for analyzing 2 x 2 contingency tables.

Na-K Pump Ratio in Erythrocytes. A. Hobbs, LMC, NINCDS. Human myotonic dystrophy is a disease characterized by muscle weakness and degeneration as well as a tendency for the muscle to discharge repetitive action potentials. Comparison of the Na-K pump ratios in erythrocytes in patients with myotonic dystrophry with that of a control group was made. Statistical procedures used were Student's t-test and the F-test.

Laboratory Animal Medicine Competency. C. McPherson, DVM, DRR. A questionnaire was sent to a random sample of 124 veterinarians to determine the requirements for labotatory animal medicine competency for graduating veterinary students. Statistical procedures used in analyzing the results of this sample survey were analysis of variances and Duncan's multiple range test.

Numerical Analysis and Statistical Consulting. Consultation was provided to R. Marimont, IRP, NINCDS, on confidence intervals and significance tests for the parameter estimates of a linear combination of exponentials; B. Gladen, LEB, NIEHS, on numerical integration; D. Winterbourne, LCBGY, NCI, on probit analysis; M. Potter, LCBGY, NCI, on biological assay techniques; J. Slack, LCBGY, NCI, on techniques to compare regression lines; and A. Thakur, ERRB, NICHHD, on fitting a polynomial using orthogonal polynomials and unequally weighted data points.

III. PUBLICATIONS

Vierling, J. M., Shrager, R. I., Rumble, W. F., Aamodt, R., Berman, M. D., and Jones, E. A.: Incorporation of radiocopper into ceruloplasmin in normal subjects with primary biliary cirrhosis and Wilson's disease. Gastroenterology 74, 4, 652-660, 1978.

Graitson, M., and Dunham, G.: Traitement Automatique du Francasis Medical, Cahiers de Lexicologies, Vol. 30, No. 1, 1977.

Dunham, G. S., Pacak, M. G., and Pratt, A. W.: Automatic Indexing of Pathology Data, Journal of the American Society for Information Science, Vol. 29, No. 2, 1978.

Pacak, M. G., and Pratt, A. W.: Identification and Transformation of Terminal Morphemes in Medical English Part II, Methods of Information in Medicine, Vol. 17, No. 2, 1978.

Knott, Gary D.: "A Numbering system for Binary Trees", CACM, Vol. 20, No. 2, pp. 113-115, 1977.

Shapiro, M. B., Habbersett, M. C., Herman, C. J., and Smith, E.: Pattern Classification of Gynecologic Specimens Analyzed with a Flowmicrofluorometer. Presented at IEEE Conference on Pattern Recognition and Image Processing, Chicago, Ill., May 30 - June 2, 1978.

Lieblick, A. K., Symmes, D., Newman, J. D., and Shapiro, M. B.: Development of the Isolation Peep in Laboratory Bred Squirrel Monkeys. The Journal of Animal Behavior, in press.

Hutchinson, G.: Embedding and unsolvability theorems for modular lattices. Algebra Universalis 7, 47-84, 1977.

Hutchinson, G.: A duality principle for lattices and categories of modules. J. of Pure and Applied Algebra 10, 115-119, 1977.

Blum, H. and Nagel, R.: Shape description using weighted symmetric axis features. Pattern Recognition, in press.

Kamel, I. A., Cheever, A. W., Elwi, A. M., Mosimann, J. E. and Danner, R.: Schistosoma Mansoni and S. Haematobium Infections in Egypt. I. Evaluation of Techniques for Recovery of Worms and Eggs at Necropsy. The American Journal of Tropical Medicine and Hygiene. 26:696-701, 1977.

Cheever, A. W., Kamel, I. A., Elwi, A. M., Mosimann, J. E. and Danner, R.: Schistosoma Mansoni and S. Haematobium

Infections in Egypt. II. Quantitative Parasitological Findings at Necropsy. The American Journal of Tropical Medicine and Hygiene. 26:702-716, 1977.

Cheever, A. W., Kamel, I. A., Elwi, A. M., Mosimann, J. E., Danner, R. and Sippel, J. E.: Schistosoma Mansoni and S. Haematobium Infections in Egypt. III. Extrahepatic Pathology. The American Journal of Tropical Medicine and Hygiene. 27:55-75, 1977.

Mosimann, J. E. and James, F. C.: New Statistical Methods for Allometry with Application to Florida Red-winged Blackbirds. Evolution, in press.

Mosimann, J. E., Malley, J. D., Cheever, A. W. and Clark, C. B.: Size and Shape Analysis of Schistosome Egg-Counts in Egyptian Autopsy Data. Biometrics, in press.

Kamel, I. A., Elwi, A. M., Cheever, A. W., Mosimann, J. E. and Danner, R.: Schistosoma Mansoni and S. Haematobium Infections in Egypt. IV. Hepatic lesions. The American Journal of Tropical Medicine and Hygiene, in press.

NIH TRAINING GRANT INFORMATION - EXPENSE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00001-07 LSM

PERIOD COVERED: Oct. 1, 1977 through Sept. 30, 1978

TITLE OF PROJECT (40 characters or less)

Automated Data Processing of Medical Language

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. G. Pacak	Computer Systems Analyst	LSM DCRT
	A. W. Pratt	Director	DCRT
OTHER:	G. Dunham	Computer Programmer	LSM DCRT
	S. Harper	Computer Programmer	LSM DCRT
	M. DeMeyts-Graitson	Guest Worker	LSM DCRT

COOPERATING UNITS (if any)

LAB/DIVISION: Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION: Medical Information Science Section

INSTITUTE AND LOCATION: Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The major objective of the project is to develop a formal and practical basis for a lexicon of the language of medicine. This must include the possibility of specialty microglossaries, morphosemantic and syntactic paraphrase rules for automatic recognition of synonymous noun phrases, and internal semantic structuring.

The system for information storage and retrieval of pathology data in natural language was maintained for future use.

Project Description:

Work on the infectious disease nomenclature as a paradigm case for morphosemantic analysis of the compound words of medical language was continued. A draft publication was prepared describing: the results of distributional analysis, the -ITIS alloforms, and a paraphrase algorithm for synonymous expressions in this nomenclature. Analogous work is in progress for French.

Research on the metalanguage for medical lexicons focused on the neglected relation between the lexicon and syntax. Areas of study included: the representation of medical language information for its actual clinical and scientific uses, morphosemantic analysis and paraphrase, parts of speech both semantically and syntactically based, convenient rule notations sufficient to describe the linguistic processes and reducible to efficient automation, the sharing of inference capabilities between grammar and the lexicon. Several internal reports were produced.

Dissemination of computer based medical lexicons was made to 4 extramural institutions and 2 users within NIH.

A data base for morphosemantic and morphosyntactic analysis of medical French was extracted from multiple sources.

An interactive "frame" or "menu selection" language data collection system was constructed as a tool for nomenclature building and its simultaneous study.

Future Efforts:

1) Completion of work on the infectious disease nomenclature and generalization of these findings to morphosemantic analysis of other groups of medical compounds.
2) Refinements of grammar rules and further development of the metalanguage for semantic and syntactic structuring of the computer oriented medical lexicon.
3) Prepare previously collected French morphosemantic data for automated linguistic analysis.

Publications:

Graitson, M., and Dunham, G.: Traitement Automatique du Francasis Medical, Cahiers de Lexicologie, Vol. 30, No. 1, 1977.

Pratt, A. W.: The Use of Categorized Nomenclatures for Representing Medical Statements, in Computational Linguistics in Medicine, Schneider, W., and Sagvall-Hein eds., North-Holland Publishing Co., Amsterdam, 1977, pp. 45-53.

Dunham, G. S., Pacak, M. G., and Pratt, A. W.: Automatic Indexing of Pathology Data, Journal of the American Society for Information Science, Vol. 29, No. 2, 1978.

Pacak, M. G., and Pratt, A. W.: Identification and Transformation of Terminal Morphemes in Medical English Part II, Methods of Information in Medicine, Vol. 17, No. 2, 1978.

SUPPLEMENTARY COVERAGE INFORMATION FOR PROJECT AS SEEN (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00012-06 LSM

PERIOD COVERED
Oct. 1, 1977 through Sept. 30, 1978

TITLE OF PROJECT (80 characters or less)

Biological and Visual Shape

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. Blum	Res. Gen. Phys. Scientist	LSM DCRT
OTHER:	R. L. Webber	Chief, Clin. Invest. Branch	CIB NIDR
	R. Nagel	Senior Staff Fellow	CIB NIDR

COOPERATING UNITS (if any)

DMG, CIB, NIDR

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.9	0.9	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project develops and applies a new geometry of biological shape that gives a natural and efficient description to a variety of biological objects at vastly differing levels: chromosomes, cells, organs, organisms.

Applications are to (1) automation of shape analysis for diagnosis and taxonomy (2) the psychology and neurophysiology of shape processes in vision and (3) the description and understanding of organ and organismic development.

Project Description:

The overall objective of this project is to develop a formal descriptive language natural to biological shapes and apply this language to the variety of problems arising in main areas of biology and medicine: taxonomy, neurobiology and organismic development. This would permit a better modeling and understanding of these processes and also allow for the automation of many shape processes now done by humans.

The methods employed stem primarily from a new geometry based on growth as the primitive process, and conceived by the principal investigator. It is applied to a variety of problems, both to clarify the biological processes taking place and to develop the mathematics in new biologically relevant directions. These include cell and tissue description from light microscopy, shape descriptions of developing organisms, chromosome description, visual psychophysics and visual neurophysiology.

Computer programs for symmetric axis analysis of arbitrary two-dimensional shapes were improved by giving added flexibility to users and addition of new output options. Studies of error introduced by quantizing continuous shapes are continuing. Investigations of interpolation algorithms, differential geometry and minimal energy considerations for curves, and information of boundary point sets are continuing.

A general method for extracting symmetric axis descriptions and for detecting edges in gray-scale pictures is still under development.

Symmetric axis methods were applied to a study of growth and development of the human mandible.

Publications:

Blum, H. and Nagel, R.: Shape description using weighted symmetric axis features. Pattern Recognition, in press.

INTERAGENCY SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00011-04 LSM

PERIOD COVERED

Oct. 1, 1977 through Sept. 30, 1978

TITLE OF PROJECT (80 characters or less)

Discrete Mathematics and Applications

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. A. Hutchinson Research Mathematician LSM DCRT

COOPERATING UNITS (if any)

NONE

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Biomathematics and Computer Science Section

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A complete formal logic generalizing equational logic as applied to group theory, the theory of vector spaces, and related algebraic theories was developed.

Project Description:

Objectives:

The project objective is to develop mathematical theory and computational techniques using discrete mathematics (algebra, combinatorics and graph theory), and to apply such methods to appropriate problems of biomedical research and computer science.

Methods Employed and Major Findings:

Groups and vector spaces are standard mathematical tools used in various fields of physics, chemistry, and other exact, theoretical sciences. A system of formal logic applying to many questions of group theory, vector space theory, ring theory, and related theories was developed. This system is a generalization of equational logic for these theories, and proofs are obtained by manipulation of algebraic expressions as in equational logic. This is, the formulas in question are free of logical connectives and logical quantifiers, and the formal proofs in this theory tend to be short and easy to follow. The system developed here is broader than equational logic, having the additional capability of dealing with questions concerning normal subgroups of groups, subspaces of vector spaces, ideals of rings, and so on. The major result proved about this formal logic is its completeness: a formula of this type is provable by the formal methods if and only if it is true for all algebraic structures under consideration. For example, a formula describing a property of groups has a formal proof in this logic if and only if it is true for all groups.

Significance to Biomedical Research and the Program of the Division:

General purpose mathematical techniques and computer programs implementing them are made available to the biomedical research community.

Proposed Course:

Work is continuing on theoretical studies to develop new computer methods and improve existing methods.

Publications:

*Hutchinson, G.: Embedding and unsolvability theorems for modular lattices. Algebra Universalis 7, 47-84, 1977.

*Hutchinson, G.: A duality principle for lattices and categories of modules. J. of Pure and Applied Algebra 10, 115-119, 1977.

(* Reported as in press in previous fiscal years.)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (DO NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00039-01 LSM

PERIOD COVERED

Oct. 1, 1977 through Sept. 30, 1978

TITLE OF PROJECT (80 characters or less)

Linear Methods in Statistics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: J. D. Malley Staff Fellow LSM DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION

Statistical Methodology Section

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (300 words or less - underline keywords)

Linear methods in statistics are being studied, with the general linear model serving as a point of departure. Family confidence limits for ratios of sample means from multivariate normal distributions were developed. The methods have utility in size and shape studies (see the multivariate statistical analysis intramural research project report) as well as in any study where ratios of normal means are important. Theoretical work in linear algebraic groups continued, and a paper on the relation between algebraic structure and automorphism groups is in preparation.

Project Description:

The overall objective of this project is the study of linear methods in statistical analyses. During the past year, in addition to family confidence limits for ratios of normal means, and work in automorphism groups and algebras, the linear methods were utilized in the understudy of log linear models for contingency tables.

Publications: None

NIH OFFICIAL SCIENCE INFORMATION SYSTEM PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00013-04 LSM

PERIOD COVERED
Oct. 1, 1977 through Sept. 30, 1978

TITLE OF PROJECT (40 characters or less)

Multivariate Statistical Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. E. Mosimann	Chief	LSM DCRT
OTHER:	J. D. Malley	Staff Fellow	LSM DCRT
	R. N. Danner	Computer Systems Analyst	LSM DCRT
	C. B. Clark	Computer Systems Analyst	LSM DCRT
	I. R. James	CSIRO, Melbourne, Australia	
	F. C. James	Florida State University, Tallahassee	

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Office of the Chief, LSM, DCRT

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Multivariate statistical methods (size-shape methods) for analyzing ratios which follow a lognormal distribution have been developed. Exact statistical tests have been developed and applied in two biological studies: the distribution of schistosome eggs in man at autopsy; morphological measurements of birds (see publications). Work on the theoretical meaning of size-shape concepts for statistical distributions continued, with a new characterization of the Dirichlet distribution being given by Ian James and Mosimann. Work on separating error effects from model effects by using information in the sample mean vector along with the covariance matrix, was begun with the work on schistosome egg counts. This work has been continued by Malley, who has analyzed organ weight data in laboratory rats.

Project Description:

The overall objective of this project is the study of multivariate statistical methods for the analysis of data which take the form of ratios or proportions. During this past year there was continued development of statistical tests and study of data. These included data of A. Cheever, NIAID, on the distribution of schistosome eggs by organ at autopsy, data on morphological measurements of birds of F. James, NSF, (currently with Florida State University) as well as data on organ weights of laboratory rats. Lectures on this work were given by Mosimann at l'Universite de Montreal (Pierre Robillard Memorial Lecture), and the University of Parma, Italy.

Publications:

Cheever, A. W., Kamel, I. A., Elwi, A. M., Mosimann, J. E. and Danner, R.: Schistosoma Mansoni and S. Haematobium Infections in Egypt. II. Quantitative Parasitological Findings at Necropsy. The American Journal of Tropical Medicine and Hygiene. 26:702-716, 1977.

Mosimann, J. E. and James, F. C.: New Statistical Methods for Allometry with Application to Florida Red-winged Blackbirds. Evolution, in press.

Mosimann, J. E., Malley, J. D., Cheever, A. W. and Clark, C. B.: Size and Shape Analysis of Schistosome Egg-Counts in Egyptian Autopsy Data. Biometrics, in press.

INTERAGENCY RECORDS OF INFORMATION EXCHANGE PROJECT NUMBER (DO NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00010-02 LS

PERIOD COVERED
Oct. 1, 1977 through Sept. 30, 1978

TITLE OF PROJECT (80 characters or less)

Nonlinear Equations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. I. Shrager	Mathematician	LSM DCRT
OTHER:	G. D. Knott	Computer Specialist	LSM DCRT
	E. Hill	Mathematician	LAS DCRT
	J. E. Fletcher	Research Mathematician	LAS DCRT

COOPERATING UNITS (if any)

LAS, DCRT

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Methods are developed for solving nonlinear equations frequently encountered at NIH, usually in the context of constrained nonlinear least squares or in the solution to nonlinear differential equations. Related problems, such as asymptotic error analysis, and the efficient treatment of sparse systems, are also considered.

Project Description:

Objectives:

To develop methods for solving nonlinear equations frequently encountered at NIH.

Methods:

A continuing effort is made to create methods or extend existing methods to solve problems in a host of NIH applications, and to house those methods in accessible computer programs or routines. Modelaide and MLAB are two examples.

Major Findings:

The Levenberg-Marquardt method for non-linear least squares, and the variant of R. I. Shrager which handles linearly constrainted parameters, have been extended to the L_1 and L_∞ norms. Revision of the manuscript is now in progress.

The MLAB curve-fitting routine has been improved, convergence is accelerated so that solutions can be found with fewer iterations and function evaluations.

The MLAB differential equation solver is being revised to take less space, on the average, for partial derivative formulas. Among the schemes being considered are

1) including an equation in the stiff set only when accuracy and desired step size seem to demand it.
2) evaluating some partial derivatives numerically.

Significance to Biomedical Research:

These methods are now being applied to problems in human metabolism, cell growth, chemical kinetics, and spectral analysis (UV, IR, CD, ORD, NMR, ESR).

Proposed Course:

As the methods are proved in test and practice, they will be incorporated into easy-to-use systems like MLAB, and as a result, the systems themselves should evolve to do more useful work with less human and machine effort.

Publications:

Vierling, J. M., Shrager, R. I., Rumble, W. F., Aamodt, R., Berman, M. D., and Jones, E. A.: Incorporation of radiocopper into ceruloplasmin in normal subjects with primary biliary cirrhosis and Wilson's disease. Gastroenterology 74, 4, 652-660, 1978.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00008-04 LSM

PERIOD COVERED Oct. 1, 1977 through Sept. 30, 1978

TITLE OF PROJECT (80 characters or less)

Pattern Recognition

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Shapiro	Research Mathematician	LSM DCRT
OTHER:	C. Herman	Senior Surgeon	LP NCI
	M. Cassidy	Biologist	LP NCI
	D. Symmes	Section Chief	BB CH
	J. Newman	Scientist	BB CH
	A. Lieblick	Scientist	BB CH

COOPERATING UNITS (if any)

Laboratory of Pathology, NCI

LAB/BRANCH Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION Biomathematics and Computer Science Section

INSTITUTE AND LOCATION Division of Computer Research and Technology, NIH, Bethesda, Md. 20014

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Computer pattern recognition methods have been developed for general use and have been applied in two problem areas.

1. C-LAB, 2nd edition.

An extensive revision of C-LAB, a system for Cluster Analysis, has been undertaken to add some important algorithms, make improvements on existing ones, make the manual clearer, and to keep up-to-date with MLAB, with which it is compatible.

2. Pattern recognition of monkey vocalization records.

Studies of similarities in vocalization patterns were completed and published.

3. Detection of cervical cancer using flowmicrofluorometer data.

An algorithm for classifying data produced by a flowmicrofluorometer, an instrument which makes measurements on individual cells, was developed based on 209 samples collected in phase I of the study.

Project Description:

Objectives:

The main objective is to provide an easy-to-use package of pattern recognition programs for the use of NIH researchers and to apply these and similar techniques to particular problem areas.

Methods:

The standard pattern recognition methods plus some of the most recent work has been programmed and applied in a number of problem areas.

Significance to Biomedical Research:

Pattern recognition techniques are now being widely used on biomedical data for classifying objects, finding relationships between variables, and for processing biological images. These applications of artificial intelligence has led to both automatic processing and a better understanding of data.

Proposed Course:

A wider range of pattern recognition and algorithms will continue to be developed and applied.

Publications:

Shapiro, M. B., Habbersett, M. C., Herman, C. J., and Smith, E.: Pattern Classification of Gynecologic Specimens Analyzed with a Flowmicrofluorometer. Presented at IEEE Conference on Pattern Recognition and Image Processing, Chicago, Ill., May 30 - June 2, 1978.

Lieblick, A. K., Symmes, D., Newman, J. D., and Shapiro, M. B.: Development of the Isolation Peep in Laboratory Bred Squirrel Monkeys. Accepted for Publication in The Journal of Animal Behavior.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00009-04 LSM

PERIOD COVERED
Oct. 1, 1977 through Sept. 30, 1978

TITLE OF PROJECT (80 characters or less)

Research Topics in Computer Science

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. D. Knott Computer Specialist LSM DCRT

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology (LSM)

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, Md. 20014

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.4	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Various storage and retrieval algorithms have been studied. The development of flexible and efficient storage and retrieval algorithms is very useful, since such algorithms are used in almost all computer programs. Thus biomedical computation in particular can benefit from improved storage and retrieval methods.

Currently, an exhaustive survey of storage and retrieval methods is underway. This includes the recently introduced k-d tree method.

Optimal item orderings in split hashing schemes and certain interesting algebraic characterizations of fixed permutation open addressing methods are also being studied. Research on trie methods are also being conducted.

Project Description:

The object of this project is to develop theoretical bases for new computer methods which will expand and improve the use of computing in biomedical computation. The methods used are the application of known algorithms and the development of new pertinent theorems involving combinatoric and other related mathematics. Research work in storage and retrieval algorithms and their efficiency has been the primary topic of concern.

Currently, an exhaustive survey of storage and retrieval methods is underway. This includes the recently introduced k-d tree method. Various improvements and refinements in both the algorithms, and their analysis, are being studied.

Optimal item orderings in split hashing schemes and certain interesting algebraic characterizations of fixed permutation open addressing methods are also being studied.

Research on trie methods, which involves storing items in trees so that the path to the item is determined by its key, is underway as well.

Publications:

Knott, Gary D.: "A Numbering system for Binary Trees", CACM, Vol. 20, No. 2, pp. 113-115, 1977.

October 1, 1977 through September 30, 1978

NATIONAL INSTITUTES OF HEALTH

Division of Computer Research and Technology

1. Summary of Branch Activities

2. DATA MANAGEMENT BRANCH

3. J. Emmett Hard
Branch Chief

I. SUMMARY

Mission and Function

The Data Management Branch (DMB) provides advice and assistance to research investigators, program officials and administrators throughout NIH in planning for and obtaining computer data processing services. In this role the branch is a central NIH resource for computer systems analysis, design and programming.

Scope of Activities

DMB staff design and create computer-based data management systems for specific users and train those users. They also teach courses about some data management and programming tools, provide advice on data management techniques to NIH programmers and serve as consultants on computer based systems proposed by other NIH groups for implementation by contractors. Finally, DMB creates and maintains general purpose, user-oriented programming tools to speed building and improve operation of specific applications systems.

Design Philosophy

Many computer applications are straightforward. Others involve an extended period of exploration to define the users needs, the appropriate information processing techniques and the computer methods best suited to the users' circumstances. Clients pay for DMB work under the NIH service and supply fund as well as for running the completed systems in the NIH Computer Center. Therefore, the DMB approach to projects can best be described as conservative but progressive using, when possible, existing programming tools to minimize development time and costs and to maximize system reliability and ease of maintenance.

The branch develops most systems for operation by the requesting organization. This places control of the completed computer application in the hands of the user, assures each user operational independence from DMB and frees the branch to work on new projects.

Experience shows that large complex projects, involving many users, may flounder for organizational and sociological reasons, as often as technical reasons. Fortunately special planning, training the users, and care in implementation of the system can avoid many of the difficulties.

FY78 Highlights

In FY78 DMB again worked on more than one hundred projects involving virtually every Bureau, Institute and Division of the NIH. Over 45% were projects for applications in-patient care, clinical research, or epidemiology; more than 12% for laboratory research areas; almost 35% for program direction, management and administration; approximately 3% for biomedical communications and 5% for development of data processing and analytic tools. About 30% of the projects required less than 80 hours each of DMB work and another 30% less than 500 hours each. The project list in Section II gives a view of the breadth of the DMB work. The following items highlight a few areas of particular interest:

The two largest efforts in the Data Management Branch this fiscal year were the Materiel Management System and the Clinical Information Utility. They represent four and three man years respectively.

The first phase of the Materiel Management System (MMS) was implemented in January, 1978. This implementation can best be characterized as a procurement control system, which enables data entry and edit of the approximately 250,000 orders generated each year. The primary outputs of this phase are (1) Printed Purchase Orders, (2) FEDSTRIP order cards for the General Services Administration, (3) Order Reports for DFM and (4) Obligation Transactions for the Central Accounting System. Although Phase I does not represent a panacea for NIH procurement and payment problems, it does create a base on which to begin addressing them constructively.

As the first step in what is projected to be full data base support for all administrative computer systems at the NIH, Phase I of the MMS demonstrates that a building

block approach to database management is appropriate and that administrative staff is capable of easily shifting from a clerical system to an on-line computer data entry system.

The Clinical Information Utility provided answers to over 240 inquiries this year. The combined databases proved both flexible and highly useful as an information source and the addition of some simple statistical analysis software rendered the response to many inquiries much more usable.

The primary programming effort in the Clinical Information Utility was directed toward the Medical Information System (MIS) purge data. When patients are discharged from the Clinical Center their data, which are collected and displayed by the MIS, are purged from that system, written onto magnetic tapes and mailed to DCRT for archiving.

After some preliminary analysis was done to determine which data elements were to be archived, programs were developed using a very simple pattern recognition algorithm to select the desired data. As the number of users increased on the MIS and the older users became more knowledgeable about the system, new MIS data collection screens were used to input new medical data which had not been included in our original design. Consequently, the pattern recognition algorithm failed to select all of the desired data.

A new pattern recognition algorithm has been designed and developed to process two classes of purge data: known patterns to be archived and known patterns which are not to be processed. This leaves a third class of purge data which is the unknown. The unknown patterns are analyzed to determine which of the previous two classes they belong. Once the class has been determined the pattern recognition algorithm is modified to process the new purge data.

Another significant improvement of the CIU this year was the patient profile. A system of programs was defined and developed to display in an orderly format all of the computerized clinical information available for any patient. The purpose of this system is to aid the physician in analyzing the previously collected data on a readmitted patient.

A Surgical Pathology System was implemented last year for the Laboratory of Pathology, NCI. Data collected by the Surgical Pathology and Postmortem Section have been included in this file since January, 1977. Final diagnoses are hand coded using the Systemized Nomenclature of Medicine (SNOMED) and patient information may be retrieved from this file using Boolean selections of the encoded diagnoses. This year data from the Hematopathology area have been added to the system. Plans call for (1) making these data available as part of the Clinical Information Utility and (2) adding of retrospective data in the surgical pathology and postmortem area.

Several other DMB projects deserve attention as examples of the variety of work performed.

As the Cardiac Valve Replacement System became fully operational this year, it became a highly useful information source for some fifty inquiries. Typical among these inquiries were areas such as morbidity and mortality of similar patient populations and survival rate comparisons among patient populations. For example, a physician might wish to analyze survival and morbidity among patients who have had a valve replaced since 1972 and have pure mitral stenosis with no other valve lesions. Response to this request is easily provided within the working day by a computer technician in the Surgery Branch, NHLBI.

The success of this system in the Surgery Branch has impelled the Cardiology Branch to begin a similar effort for its patients. The Cardiology Branch is able to take advantage of our previous experience and should have an operational system by mid-summer of 1978.

The Reproduction Research Branch of NICHD is involved in the preparation of purified proteins (hemoglobin, albumin, hormones) by the process of gel electrophoresis. Using a scanning isoelectric focusing assembly (Catsimpoolis Apparatus) it is possible to obtain, across time, quantitative data on the position, bandwidth, peaks, etc. of the protein as it filters through the gel. This physical/chemical data can provide information which enables researchers to determine rules controlling the behavior of the proteins in the gel and to enable them to refine their purification procedures.

Working closely with the research scientist, DMB developed an interactive system for performing the statistical analysis and displaying peaks, which can interface with a non-computer oriented user. Currently, work is progressing on a method for automatically choosing the tolerances for peak detection.

In an effort to assist in the data reduction and analysis of scintillation counter data, DMB has begun the development of a set of standard computer programs. These programs will run on the PDP-10 computer and should answer the needs of a large percentage of scientists who may use the liquid scintillation counter data logger developed by the DCRT Computer Systems Laboratory. The needs range between two extremes. Some scientists want a set of programs to perform fixed functions on a routine production basis. Others could use an interactive system to perform exploratory data analyses and then perhaps statistical testing and curve fitting for on-line model development.

The liquid scintillation counter applications thought to be in most need of automation are radioimmunoassay, chromatography and electrophoresis, interactive graphics channel ratios and spillover and quench corrections, and adenylate cylase activity calculations.

During FY77-78 we produced an interactive working version of a self-teaching system which takes care of most of the problems encountered in Chromatographic-Electrophoresis (except automatic peak detection) and which can draw plots on any of a number of devices including the DEC-340 visual display and the teletype. Subsequently these plots can be sent directly to the CalComp for offline plotting. At present, work is being done on a "mini M-Lab" type of peak detection module which will allow the user to check and modify the results of the program interactively.

Drug induced heart failure limits the use of adriamycin as an anticancer drug. By identifying the risk factors which attach to adriamycin therapy one can administer this drug more effectively and at the same time provide a reasonable margin of safety for the cancer patient. In the previous fiscal year, the adriamycin toxicity study, a cooperative effort among the Investigational Drug Branch and Biometry Branch of the NCI and the Data Management Branch, was begun. Since that time data on 4018 patients has been collected and twelve risk factors have been identified. It is anticipated that one can use these known factors to estimate patient risk and to adjust adriamycin therapy prospectively.

Future Plans

In FY79 and the foreseeable future, DMB will pursue the same direction that has proven successful over the last few years. There is still a clear need for a central NIH resource for advice, consultation, systems analysis, design and programming on data management applications of computers. The DMB staff has accumulated a wealth of experience in developing NIH data management applications on the NIH Computer Center systems. It has a reputation for reliable, effective work. It has a powerful set of tools to generate new applications and works with experts in other DCRT laboratories when more complex statistical/mathematical analyses and/or engineering skills are required to satisfy a specific need.

DMB projects will continue to arise from the data processing needs of NIH, a remarkable mix in size and substance. The best solution/system for a given problem/project will, of course, depend on the technology available at the time it is undertaken. The prospect of "intelligent" terminals, as well as more powerful software, mean only that more options will be available, not that a given user will get a more complicated or expensive solution/system. Nevertheless, some data processing needs at NIH will undoubtedly lead to more ambitious projects.

During the FY78 the Data Management Branch assumed responsibility for new development of all central financial systems at the NIH. This new development will follow the general approach used for the Materiel Management System, i.e. modular database design and full integration with the existing database system. No new development will occur until agreements can be reached on the maintenance of the existing accounting system and the methodology to be used to shift from the current accounting application to a database design concept.

Phase II of the Materiel Management System is planned for implementation by December, 1978. This phase will complete the receiving and payment cycle.

The Clinical Support Section plans to continue improving and developing the Clinical Information Utility. The development work will be done mainly on the archiving procedure for low activity data and the addition of new clinical information databases. In the improvement area the section will continue to reduce the cost of updating and retrieving data for those systems.

When the DMB completes development of the Patient Record System for the Cardiology Branch, NHLBI, it is intended that this file be merged with that of the Surgery Branch, NHLBI. This integration should result in a highly useful database for patient care and clinical research for both branches.

Work has recently begun on a radiation safety control system for NIH. This will enable (1) Control of order, receipt and inventory of all radionuclides at NIH, (2) Maintenance of a training record on all persons, who handle radioactive material and (3) Gathering and reporting of all contractor survey data relating to laboratories which handle radioactive material and (4) Updating of wastes processing and activity balancing. Work has begun on the first two systems and is scheduled for implementation in the Fall of 1979.

II. PROJECT LIST

The list below does not include a number of small new projects and modest revisions and additions to existing systems. These become literally to numerous to mention in an annual report although each is clearly important to the client and requires careful work by the DMB staff.

A. Clinical Research, Patient Care and Epidemiology

1. Retrospective Study of Cardiac Valve Replacement

In 1975 the Data Management Branch began development of a computerized data processing system for the Clinical Surgery Branch, NHLBI. The system was called the Retrospective Study of Cardiac Valve Replacements. The object was to design a system which could maintain all pertinent information on heart valve replacement patients and assist the Clinical Surgery Branch in the processing of this data in an attempt to define the morbidity and mortality of patients who underwent the open heart surgery, and to evaluate the various procedures and valves. The system became fully operational in 1977 and has proven to be a valuable source of information for NHLBI investigators.

2. Computerized Patient Record System for Cardiology

Work on this system for the Cardiology Branch, NHLBI began during this year. The system and database structure are the same as that of the Surgery Branch system. The system maintains patient medical information for both in-patients and out-patients.

The system will become operational in mid-summer 1978. At that time the Surgery Branch system and the Cardiology Branch system will be combined to produce a single system and database to serve both branches. This will provide for more complete data and reduced maintenance effort.

The combined database will maintain such information as operative notes, narrative summary of follow-up sheets and office chart, admissions, patient relatives reference, nuclear angiogram, EKG, X-ray, echo-cardiogram, operations not at NIH, hospitalizations not at NIH, catheterization, clinical visits, pacemakers, diagnosis, and autopsy.

It is anticipated that the combined system will be operational by early 1979.

3. Analysis of Cardiac Valve Data

This project for the Surgery Branch, NHLBI, consists of special statistical studies or the graphic presentation of results on the database created under the Retrospective Cardiac Valve Replacement Study. Most of the studies this year were calculations of survival times and survival probabilities.

(1) Eleven multiple-line CALCOMP plots were generated to present graphically the survival time differences of various experimental groupings of the 138 MVR (Mitral Valve Replacement) patients. The MVR's were of both porcine and mechanical types. The cumulative survival probabilities (classical computation scheme) of groups with differing PA systemic pressures, RA mean pressures, occurrences of mitral stenosis and regurgitation were computed and displayed. Also presented were the survival probabilities for the isolated MVR group versus those probabilities. A significant finding was generally longer survival time of the procine valve users as opposed to the mechanical users.

(2) A number of program outputs were prepared for a set of 33 patients who had undergone at least two MVR's. The outputs included the following:

a) A printed formatted dump of selected clinical data fields.
b) Descriptive and correlational statistics for the computed survival time, interval between operations, and age variables.
c) A printout of mean survival times for various age and sex categories.
d) Multiple-line CALCOMP plots depicting the mean survival time for various categories of age, sex, functional class, and status (dead, lost). This was a graphic presentation of c) with the functional class variable added.
e) Printer plots displayed the 33 individual survival times versus the interval between operations.
f) CALCOMP plots of functional class population counts versus times of function class assignments (pre-op 1, post-op 2, pre-op 2, post-op 2, or last visit).

Future Needs - Incoming requests will be evaluated as needs arise in the Surgery Branch that would further test the valves in relation to survival time of various categories.

4. Study of Chemistry Data from Survey Participants, College of Clinical Pathologists

This collaborative study with the DCBT Laboratory of Applied Studies uses data from the 1975 Comprehensive Chemistry Survey collected by the College of American Pathologists, Traverse City, Michigan. The data represented are for Calcium, Glucose, and Chloride. The dataset includes results only from the participants who provided a full set of 12 values and who used the same method on all specimens.

Programs were completed to edit and compute some statistical parameters. Following a thorough review of the computed parameters, a detailed analysis was completed to test the differences between chemical methods using the Kruskal Wallis techniques.

5. Serum Pool Evaluation

This collaborative study with LAS involves pooling blood samples of many patients and reading the pooled chemical results. This pooling was performed over a three-month period in weekly intervals. The analysis of this data will reveal effects of variation of analytic methods over time and will be used as quality control in comparing and evaluating other groups.

Completed to date are programs that would compute Time Trend Analysis using the Mean-squared Successive Differences approach. Since some unexpected fluctuations have been revealed, evaluation of the slope over time was analyzed.

6. Analysis of SLE Nephritis Patients

This is a collaborative research project including LAS of DCRT and ARB (Arthritis and Rheumatism Branch), NIAMDD. A system was developed to store chemistry and therapy data on all SLE (Systemic Lupus Erythematosus) nephritis patients participating in ARB studies from November, 1969, through November, 1976. Patient Data is stored by categories: i.e. Dating of Clinical Manifestation, Therapy, Objective Information, Lab Data, Complications, etc. Each category of information contains subcategories of information. For example, under the "Objective Information", the subcategories include: skin biopsy, parotid flow rate, lip biopsy, parotid scan, brain scan, bone marrow, etc. The system also will allow multiple entries of all items.

The clinical chemistry data, urine data, and the hematology data will be supplied by the Clinical Support Section from the Clinical Information Utility.

7. Work-Able Cancer Patients Employment Studies

This study for the Division of Cancer Control and Rehabilitation, NCI, involves pooling of numerous sub-data bases prepared by contractors in different locations for tumor registry. Each contractor Data Base includes survey questionnaires (responses from work-able cancer patients and their employers). Editing of the responses and the frequency of each of the patients' employer responses have been completed.

So far our analysis has revealed certain inconsistencies among the data submitted by different contractors. These inconsistencies are being resolved.

The major remaining task is to compare and evaluate patient versus employer responses, as well as responses among different geographical locations.

8. Use of Population Distribution to Improve Estimation of Individual Means in Epidemiological Studies

This study with LAS, DCRT examines the properties of clinical chemistry data which might help to improve the accuracy of observed values as estimates of the true means of individuals. This procedure uses the weighted average to replace observed values using the population mean and using the Empirical Bayes estimates.

9. Penetrating Head Injury Study

A computerized data processing system was developed for the Chief of Laboratory of Experimental Neurology, NINCDS, to maintain and query a database consisting of medical data on American military men sustaining penetrating head injuries in the Viet Nam war. The data maintenance portion of the system became fully operational during this year. Evaluation and analysis of the data is continuing to be handled by the Physical Sciences Laboratory, DCRT.

10. NIMH Clinical Research Data Management System

An on-line data management system has been proposed by Dr. Buchsbaum for use with clinical research data at NIMH. At present, different researchers maintain different files, eventhough the same group of patients is involved in the different research projects. Each researcher incorporates into his own file that data which is pertinent to his own study. Consequently, data is fragmented and duplicated, file maintenance is difficult, and data integrity is doubtful. It is desirable therefore to develop a standard on-line data system for use within the NIMH and, if possible, make such a system adaptable for general use in other clinical research environments.

The proposed system would be similar to systems offered by commercial time-sharing companies. It would include facilities for data entry, updating, reformatting, retrieval, and statistics and would be oriented toward use with small scientific databases. Specifications for the system have been approved, and DMB has undertaken implementation as a long-term development project.

11. Purge Data System

A pattern recognition algorithm was developed to identify two classes of purge data from the Clinical Center MIS System: Known patterns to be archived in the CIU and those patterns which are not to be processed. There is a third class of data which is unknown to the algorithm and it will be displayed during execution. The displayed class of purge data will be analyzed to determine which of the above two classes it belongs. Once the class has been determined the purge data system will be changed to process it.

12. Patient Profile System

A system of programs is being developed for the Clinical Information Utility to display a profile by patient. This profile will include all computerized data for a specific patient presently in the Clinical Information Utility. The format of the profile will be in patient number order by date.

13. Surgical Pathology System

The Surgical Pathology System was begun in 1977 for the Pathiological Anatomy Department, CC, as part of the ongoing DMB project in support of Clinical Center Data Processing. This year it was modified to include Hematopathology data from that department.

14. Sickle Cell Anemia Patients

Molecular Hematology Branch, NHLBI, is studying 20-25 sickle cell anemia patients who have entered an NIH study over the last 2 - 2 1/2 years. They are gathering information on the clinical course of the disease in order to predict the course in an individual patient. There is great variance among patients and it has been difficult to evaluate treatments.

We have built a system which integrates the DMD Update Generator for data entry by the investigator; the Clinical Information Utility system as source of lab test information; and the Symbolic Logic Retrieval System as the tool for querying the combined database. We also provide a patient history printout for use by the physician/investigator as patients re-enter the hospital.

As the usefulness of the database is explored using the facilities provided, statistical analysis requirements will be formulated and further enhancements made to the system.

15. MIS Study

The Office of the Deputy Director, Clinical Center, is doing a study of the Medical Information System to analyze its impact on patient care.

Programs have been written to plot daily system performance (number of requests and waiting time vs. time of day) to determine peak periods of usage with a view to distributing usage more evenly during the day. Consulation with LSMP provided a scoring algorithm which was implemented.

When the data is all in and run, a decision will be made as to whether more elaborate plotting would be preferred.

16. Cancer Survival System

The Survival System was originally developed in the 1960's to support the End Results in Cancer Studies of NCI. Maintenance and improvement of the system is the primary goal of this project.

During FY78 a number of MVS-related problems which arose in conjunction with certain applications of the system were resolved. We also sent the system to the Hawaii Tumor Registry.

17. Chronic Dialysis Complication Study

The staff of the Artificial Kidney-Chronic Uremia program, NIAMDD, is assessing the frequency of various complications of chronic renal diseases in order to better direct research efforts to areas of maximum benefit in improvement of therapy.

To aid in this they have selected five major dialysis centers widely scattered over the U.S. and are reviewing hospitalization records of chronic renal failure patients (patients on dialysis) during the year 1976.

During the past fiscal year we completed the database creation and produced a clean file for analysis. LSMI is currently providing the statistical support for this project.

18. Cryptococcal Meningitis

The Office of the Scientific Director, NIAID, was following some meningitis patients using the CDC-31 computer in the Clinical Center. With the follow-up information coming in and with the demise of the CDC-31, it was necessary to convert the programs and data to the IBM 370. Conversion and restructuring of programs took place in time to allow updated results to be presented at a meeting of the Infectious Disease Society and the International Congress of Antibiotics and Chemotherapy.

19. Analysis of Risk Factors for the Development of Adriamycin (A) - Induced Conjective Heart Failure

The Adriamycin Toxicity project was begun in FY77 for the Cancer Therapy Evaluation Program, NCI. During FY78 data entry and initial analysis for U.S. patients was completed. An additional four hundred patients under the age of ten will be added to the Adriamycin Toxicity study. This will serve to broaden the risk factor analysis base for this group of patients. Follow-up information will also be added for all patients currently on file. Dr. Van Hoff, the principal investigator on this project, is also gathering data on European patients and these will be added to the file during this coming fiscal year. There is also some discussion on establishing an adriamycin clearinghouse to provide doctors with risk factor analysis for individual patients.

20. NIAMDD Study of the Incidence and Prevalence of Kidney and Urinary Tract Diseases in the Armed Forces

This study was begun in 1974 for the Kidney Disease Program, NIAMDD, to evaluate the occurrence, morbidity and mortality of kidney and urinary tract diseases in an effort to determine research needs. Data for the study was made available by the Air Force, Army and Navy. There has been difficulty in obtaining correct data from the Army. We received our fourth set of data from the Army during FY78 and ran a series of reports. The data involved additional diagnosis codes and covered the years January, 1971 through June, 1977. The original data requested was for the period of January, 1971 through December, 1973. Present plans are to prepare reports using the Army data, assuming it is correct. After this is completed a decision will have to be made to either request the additional data from the Air Force and Navy or eliminate the additional data received from the Army when comparing data for the three services.

B. Laboratory Investigation

1. Survey of Chemicals Being Tested for Carcinogenicity

Early in 1978 the Carcinogenesis Testing Program, NCI, asked DMB to assist the International Agency for Research in Cancer, World Health Organization, in the development of a computerized Information Bulletin on the Survey of Chemicals being tested for Carcinogenicity.

The system should accept randomly at least nine items per record (i.e., (1) country, (2) city, (3) name and address of institute, (4) name of chemical, (5) species (strain), (6) exposures, (7) stage of experiment, (8) principal investigators, and (9) comments), sort on any of these items, generate indices, and output the report in a columnar format. The source input will come from questionnaires distributed by the World Health Organization to laboratories/institutes throughout the world.

Currently, basic system design questions are being clarified. This project will carry over into the coming year.

2. Chromatography and Electrophoresis Peak Analyzer

The Reproduction Research Branch of NICHD is involved in the preparation of purified proteins (hemoglobin, albumin, hormones) by the process of gel electrophoresis. Using a scanning isoelectric focusing assembly (Catsimpoolis Apparatus) it is possible to obtain, across time, quantitative data on the position, bandwidth, peaks, etc. of the protein as it filters through the gel. This physical/chemical data can provide information which enables researchers to determine rules controlling the behavior of the proteins in the gel and to enable them to refine their purification procedures.

Working closely over the last five years with the research scientist, DMB developed an interactive system for performing statistical analysis and displaying peaks, which can interface with a non-computer oriented user. Currently, work is progressing on a method for automatically choosing the tolerances for peak detection.

This system was presented at the Electrophoresis '78 International Conference at MIT. A journal article is now in preparation.

3. Carcinogenesis Information Evaluation

During FY78 we continued development begun in FY76 on the analysis phase of the Carcinogenesis Bioassay Data System for the Carcinogenesis Testing Program, NCI. The immediate aim is to detect previously unidentified carcinogens.

The interactive system for statistical analysis (CBDSAS) was upgraded during the year with the installation of a trend analysis module. The CBDSAS Terminal User's Manual underwent extensive revision to reflect additions to and revisions of the system.

As the results of the experiments continue to arrive at an accelerating rate, usage of this system by NCI and contractor personnel has been high.

4. Gene Mapping Program

At the Laboratory of Viral Carcinogenesis, NCI, a map of cat chromosomes is being developed with the immediate purpose of studying cat leukemia, and the long-term goal of making predictions about enzyme defective diseases.

Cloned cultures of hybrid cat-mouse cells are assayed for about 40 proteins by gel electrophoresis techniques which not only resolve the different proteins but will usually allow the determination of genotype.

A program was written this year to tabulate the degree of simultaneous activation of various gene pairs for all clones according to prescribed categories and to calculate the percent of discordancy for each protein pair. Using these pair comparisons it can be determined whether or not any two genes are on the same chromosome. Another program lists the specific clones which exhibit discordancies for any two specified enzymes.

Since a host cell will usually only have one donor chromosome, the above information collected from a sufficient variety of clones will allow investigators to determine on which chromosome each gene is located in the donor genotype and thereby map the chromosome location for the common protein.

5. Cytotoxicity

The Immunopathology Section, NCI, performs experiments to determine toxicity levels. Calculations of radioimmunoassay data were done with a hand calculator, graphs of samples plotted out by hand, and the toxicity of various biological samples read off the graph. We automated this process to run on the PDP-10. The program is general enough that it can be used for subsequent experiments. Ideas for future enhancements to the program have been discussed.

6. Genetic Marker Tracing System

This project for the Laboratory of Immunogenetics, NIAID, involves the analysis, design and creation of a system to provide the capability for tracing genetic markers within a colony of rabbits. The initial analysis, design of the data collection forms and design of the databases are completed. The file maintenance and retrieval routines

are completed and tested. The first update of the master file was run in June, 1978 and given to the user. After a few more update runs, and completion of the documentation, the system will be turned over to the user.

7. Chemical Information System

This project for the Carcinogenic Testing Program, DCI, involved the modification of an IMS system developed by Stanford Research Institute to run on the NIH/DCRT computer system. This effort was completed during the year and the system turned over to the customer for running.

8. Circadian Rhythm in Rodents

Biomedical Engineering and Instrumentation Branch (BEIB) of the Division of Research Services (DRS) is building a system that will monitor, record and report the activity level of rodents in cages. A micro-processor will record such factors as animal temperature, room temperature, room light, and level of activity within a given time period, from sensors located within each study cage. The data from the micro-processor will be transferred to the IBM-370 and stored as WYLBUR datasets, which will be used as input to an update routine.

The database has been defined and update and plotting programs have been written but testing has been limited until data can be received from the micro-processor. At the present time BEIB is having problems with the micro-processor.

9. In Vitro Information System

The In Vitro Information System (IVIS) is being developed to process information about In Vitro carcinogenesis tests conducted under the auspices of the Division of Cancer Cause and Prevention of the National Cancer Institute. IVIS may also be used to process data about tests conducted by other agencies. The system provides for the collection, maintenance, analysis and reporting of In Vitro data. Data for the system will come from contracting laboratories on input forms with both descriptive and results data. The input forms will be converted into machine readable format and be processed on

computers at the Division of Computer Research and Technology (DCRT) at NIH using the proprietary MARKIV system installed in February, 1978. Development of a system using MARKIV is in progress.

10. Mutagenic Testing System

This system will provide programs for the Environmental Biometry Branch of the National Institutes of Environmental Health Sciences to monitor the protocol for mutagenesis testing. Design specifications call for multi-terminal, on-line, conversational program package to interface with laboratory technicians and provide controlled data collection, data storage, and data analysis. During FY78 a meeting was held to demonstrate the system in a simulated operation. At that time the complete system was released for live testing as part of a current mutagenesis research contract. The mutagenesis protocol for suspension testing is under revised development.

11. Liquid Scintillation Counter Package

Now that a data logger is available to standardize liquid scintillation output for easy input to the computer, DCRT is developing, on the PDP-10, a comprehensive set of routines which can answer the needs of a reasonably large percentage of scientists who use Liquid Scintillation Counters.

During FY78 we produced an interactive working version of a self-teaching system which takes care of most of the problems encountered in Chromatographic-Electrophoresis (except automatic peak detection) and which can draw plots on any of a number of devices including the DEC-340 visual display and the teletype. Subsequently these plots can be sent directly to the CalComp for offline plotting.

At present, work is being done on a "mini K-Lab" type of peak detection module which will allow the user to check and modify the results of the program interactively.

C. Program Management and Administration

1. NIH International Activities and Personnel Monitoring System

A few years ago, the Data Management Branch implemented this system to provide the Fogarty International Center with the capability to maintain, report on and query a database covering the Visiting Program, Foreign Guest Workers and Foreign Visitors at NIH.

The system has proven valuable to the Fogarty Center. This year the system is being re-evaluated and, where appropriate, upgraded and expanded with current technology to meet current needs.

Work is being started to identify needs in several of the other Fogarty offices, with an eye toward developing individualized computerized systems for these offices, but systems which will be compatible and will complement each other.

2. Grants Information Files System

The computerized Review and Evaluation Branch (RAEB) Grants Information Files System was designed and implemented for the Division of Cancer Grants, NCI, over the last three years.

The system maintains data, answers queries and produces a variety of reports relative to NCI grants. A contracts portion of the system will be implemented next.

3. Computerized Distribution System

A computerized mailing list system was designed and implemented for the NIH Printing and Reproduction Branch.

The system of computer programs and procedures is comprised of two subsystems and their respective databases. One subsystem maintains a base of approximately fourteen thousand NIH employees. Mailing labels can be selectively produced using such information as work category, organization, grade, title, etc. as well as any of several special mailing list indicators.

The other subsystem maintains a database of about seventy five thousand outside-of-NIH individuals. Mailing labels can be selectively produced for any of the nearly seven hundred different indicators. Both subsystems provide for selection using any of the mailing list indicators in any logical combination.

This system makes it possible for the Printing and Reproduction Branch to fill requests for labels usually within twenty-four hours.

4. Library Circulation System

This system provides the DCRT Library with an improved computerized method of inventory control, circulation control and to monitor usage on an item (book, journal, etc.) basis. The system pays particular attention to ease of input, accurate and immediate status of circulation items, usage statistics, and automatic generation of overdue notices. The system controls overdues, and provides waiting lists and listings of loans by borrower. It will be used to weed out less useful and outdated materials, to aid in clearing employees leaving NIH, and to monitor the whereabouts of all materials. The programs are written and awaiting data input.

5. Consultant File Management System

The Consultant File Management System for the Review Branch of Extramural Affairs Division, NHLBI, was completed in 1978.

The system will help the Review Branch personnel organize and maintain a master file of 'consultants' from throughout the United States who participate in NHLBI site visits to various research projects in progress which are funded by NIH grants or contracts from NHLBI.

The system maintains all identification information, fields of expertise and experience, and information and history of all site visits for each consultant. It will serve as an aid in forming site-visit teams, provide correspondence assistance and make possible basic statistics on the consultant and site-visit activity.

The Review Branch is currently initializing the database. When that is completed, the system will be operational.

6. Materiel Management System

This project is concerned with the design, development and implementation of a computer based NIH-wide Materiel Management System for the purpose of improving overall operating efficiency. The system operates primarily in an on-line environment utilizing database management technology, namely IBM's Information Management System (IMS). In addition to the on-line functions, the system provides for periodic batch-processing functions to meet operational, accounting and management control requirements.

Phase I which can best be characterized as a procurement control system successfully went into production in late January. Involved in this phase is the data entry and editing of all NIH procurement orders, some 250,000 orders per year. As part of the data validation, a vendor database consisting of some 30,000 vendors who provide goods and services to the federal government is maintained. The primary output of Phase I are 1) Printed Purchase Orders to be sent to the vendor, 2) FEDSTRIP order punch cards to be sent to the General Services Administration, 3) Order Reports for Claims Review, and 4) Obligation transactions that are passed to the Central Accounting System.

Phase II, Receiving and Payment, is presently under development.

7. Animal Allocation Program

The Extramural and Collaborative Programs Group, NIA, has maintained a colony of aging rats and mice at the Charles River Breeding Laboratories in order to supply rodents of various ages to investigators studying the aging process. At present there are three animal colonies with a fourth to be added and plans to expand to eleven strains. The job of balancing future supply with present and future demand has already become almost unmanageable by hand.

NIA wanted a computerized method of: (1) projecting 30 months ahead of time the effects on the colonies of actual drones, (2) using projected draw and colony size for planning purposes.

There is now a running program which applies survival rates and projected draw to the weekly colony census figures and projects colony size for rodents up to 60 months of age as desired. This program also allows the NIA to project the effects of unexpected draws, non-routine draws, and the addition of animals to the colonies at any age group.

8. DRR Integrated Information Management System

The Office of Program Analysis, DRR, has a computer-based system for handling program data. DRR now would like more capabilities than the original design allows (e.g., interactive querying, plots, etc.) plus a more manageable update scheme. Difficulties in correlating scientific and administrative data must be resolved and a way found to provide shorter response time for filling requests.

We have been working with DRR to determine a file design and retrieval scheme which can provide them with the retrieval logic flexibility they require without sacrificing quick response time. Some decisions have been made regarding methods of implementation and work will continue during FY79.

9. Primate Reporting System

This system has been developed to control data on primates processed through the Veterinary Quarantine Unit, Office of the Director, DRS. During the fiscal year DCRT support of the Optical Character Reader (OCR) was discontinued. This necessitated designing a new form for keying and making modifications to a number of programs in the system. The system has been designed to allow for input of data either through batch keying or on-line interactively at the user's terminal. All programs for collecting, updating, editing, and reports have been completed. A Symbolic Logic Retrieval (SLR) program has also been provided for the user to answer ad hoc queries on-line. The system was turned over to the user in April, 1978.

10. Case Reports

As a result of the recommendations of the Committee on Academic Science and Engineering (COSE), these reports have been produced annually since 1965. The reports are prepared for the Division of Research Services, Office of Program Planning and Evaluation (OPPE), and summarize DHEW awards to Institutions of Higher Education, Health Professional Schools, Non-profit Hospitals, Non-profit Research Institutes and Operating Foundations, and Research and Development Centers. The data for FY77 has all been received, edited and balanced, and copies sent to the National Science Foundation (NSF). The program developed during the last fiscal year to match previous years data with the incoming data was used on all data this year and proved to be very successful in that a number of reporting component organizations were alerted to gross discrepancies and were able to recheck their records and either resubmit new or amended data. Final reports should be completed during this fiscal year.

11. System for Controlling and Monitoring Complaints of Discrimination at NIH

This system for the NIH Division of Equal Opportunity establishes a database containing information on formal and informal complaints of discrimination at the NIH to: 1) provide statistics associated with processing complaints in a more timely fashion; and 2) enable the user to more closely monitor status of complaints. Design specifications and coding formats have been developed. An update program has been written and transaction records are being collected as input to the master file. A Symbolic Logic Retrieval (SLR) program has been written to query the master file. It is hoped to implement this system during this fiscal year although data is still being collected.

12. Materiel Management System (MMS) Query and Reports

This project will determine the feasibility of using the MARKIV system to provide an economical method for the selection and reporting of data from the NIH MMS database. Four daily and two of the weekly reports produced by the MMS inquiry routine have been written in MARKIV. The MARKIV outputs are being evaluated, through parallel runs,

with the reports from the IMS Inquire. Future plans for the use of MARKIV, in conjunction with the IMS files, include the development of an audit trail file and a facility to handle ad hoc requests.

13. Division of Research Services (DRS) Activities

The Office of the Director, DRS, requested that analysis, design and programming services be provided by the DMB to:

1) Establish a job control system for the systems maintenance section (SMS) of the Biomedical Engineering and Instrumention Branch (BEIB). The system involved writing collection, update and edit, and daily and weekly report programs. The system was completed and turned over to the user in March, 1978;

2) Develop a rental information system for BEIB. The analysis and design have been completed for this system. Work in progress involves design of forms for data collection, update and edit programs, procedures for error handling, creation of an instrument Indexed Sequential Access Method (ISAM) file, and production of reports. Present plans are to start running the system, in parallel with the manual system, during this fiscal year.

14. Survey of Biohazardous Materials

The initial phase of this automated system for DRS was designed to print a questionnaire that will later be sent to all of the NIH labs. Data will be collected for each employee who is working with any biological agents, tissue cultures, etc. listed in the questionnaire. An on-line data collection program has been written and tested. Report generating programs await specifications.

15. Radiation Safety Control System

The Radiation Safety Control System for DRS will be composed of the following subsystems:

1) Inventory and Bioassay
2) Training
3) Laboratory Survey and Airborne Release
4) Waste Processed and Activity Balance

The total system should be an integrated system capable of supplying data from one subsystem to another in order to produce desired reports.

Waste Processed and Activity Balance subsystem has been undefined as yet.

The analysis and programming for the Inventory and Bioassay subsystem has been completed. We are presently awaiting the data necessary to build the control file of individuals using radionuclide materials before we can proceed. Upon completion of this file, a parallel of the new and old systems will be run to isolate any deficiencies or programming bugs. It is estimated that the new system will be supplemented in September of 1978.

A meeting was held June 1, 1978 to discuss the development of the Training subsystem. A follow-up meeting will be held June 20, 1978. The programming of the subsystem will not proceed until the Inventory and Bioassay subsystem has become operational. The Laboratory Survey and Airborne Release/Waste Processed and Activity Balance subsystems have not yet been defined. It is presumed this will occur after acceptance of the Training subsystem.

16. NIEHS Grants Management Information Network

The purpose of this project is to develop a grants management system for the Program Analysis Branch, NIEHS. This involves the creation of a Grants Management File, and creating a Retrieval and Reporting System. The Grants Management File will be created from a subset of the NIEHS Grants data available from DRG IMPAC File and administrative data to be input by PAB, NIEHS. The Retrieval and Reporting System involves hierarchical searches of Administrative Codes.

17. Provide Systems Analysis and Programming Support for NIDR Programs

This project will involve a complete analysis of the NIDR's present and anticipated future ADP system requirements. It will include the following specific short range projects.

1. Financial Management System.

2. Contract Data System.

3. Interactive On-line Project, Personnel and Financial Systems.

4. Bibliographic Citation System.

18. NIH Central Library Circulation System

This project for DRS involved the installation of a library control system purchased from the University of South Carolina on the NIH/370 system.

All programming including the modification of the USC programs is complete. The RUN procedures have been established, the entire system tested and the system documentation written.

We are currently reviewing a request for an 'In Process Materials On Order' system. It is requested that this system run interactively on the library's PDP-11/40 computer, but due to limitations of the current PDP-11/40 configurations it may be necessary to develop this, 'In Process', system on the IBM-370.

19. The National Clearinghouse for Capacity Building and Human Services Integration Program

The clearinghouse service is being provided by the Aspen Systems Corporation under a DHEW contract. In support of this effort the DMP developed systems for 1) the subscriber file; and 2) the literature file. For both systems, the necessary programs for collecting, updating, editing, printing and querying of the files were provided and the entire system along with documentation was turned over to the user during the fiscal year.

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D. Biomedical Communications Applications

1. Selective Dissemination of Information (SDI)

DMB continued support of the current awareness search for Chemical Biological Activities (CBAC). This service is still offered free of charge to all researchers at NIH and is run biweekly as tapes are received from Chemical Abstracts Service in Columbus, Ohio. Retrospective requests are being referred to the on-line service, TOXLINE, available at NLM.

DMB continued support of the current awareness search of Biosciences Information System (BIOSIS). Three times a month tapes are received from the Biological Abstracts Service and information is disseminated to the NIH community thru the same vehicle as CBAC.

Mr. C. Gillespie of the NIH Library has been the primary contact with the NIH researcher wishing to search this data base; he submits their profiles to DMB for current awareness searching, and to NLM for retrospective searching.

E. Computer Research and Technique Development

1. Inquiry and Reporting System (IRS)

IRS is a proprietary package developed by Sigma Data Corporation. During FY78 DMB continued its user support of this system. This includes maintaining the integrity of IRS by testing new IRS releases and notifying users of changes to IRS, keeping informed about DCRT hardware/software changes that may affect the operation of IRS, and providing IRS classes.

2. Recursive Macro Actuated Generator (RMAG Project)

RMAG is a programming language used for the generation of other source programming languages and Data/Text strings. The original RMAG was implemented in 1970 as a compiler i.e., a program that functioned in the mainbatch job stream of the NIH Computer Center, reading programs

written in RNAG language and generating specific programs for users. Since its implementation, several very powerful additional arithmetic and logical features were built into it, but its mode of access and use as a compiler remain the same.

In FY73 a previously developed Symbolic Logic Retrieval (SLR) system was substantially completed. Extensive documentation was produced for this powerful, interactive retrieval system.

An RNAG22 encoded generator, reading free form specifications of the user's file structure, generates a customized COBOL program which interactively retrieves selected records from the user's file. The generated COBOL program permits its user to interactively utilize sentential calculus selection schemata, implied existential quantifiers, sophisticated arithmetic specification, the RNAG22 macrogenerator, and external macro libraries. Because RNAG22 has been made a part of it, user's generated SLR is extensible at any time in the future without the need to then modify the source program.

Also in FY73 the previously developed REPORTGEN was extended to work in conjunction with SLR data files.

This product involved development of a special purpose high-level programming language for routine operations on data files. Programs can now be generated (1) to create and update files using key oriented transactions, (2) to reformat data files, and (3) to index textual data from files (file inversion). Files are assumed to have, in general, multiple logical records per subject. Any generated program can validate or error-check data in the files it reads, using conditions involving relations between fields. This year's efforts centered around extending REPORTGEN to deal with SLR "event records".

3. Autotab II

This is an easy-to-use software package designed to create and update tables of numbers. Even non-programmers can use the system, which requires only basic information (about rows, titles, column headings, initial values, and calculations needed) to produce attractive final reports. Related tables can be consolidated so that changes in one table can be 'rippled' through all others in the group.

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT

2. COMPUTER SYSTEMS LABORATORY

3. Alan M. Demmerle
Chief

I. SUMMARY

Function

The Computer Systems Laboratory (CSL) identifies and solves problems in areas of biomedical research and clinical care where real-time data collection, analysis, display and experiment control are required, where economic considerations favor a small computer or where proximity of the computing equipment to the work site is important to successful solution.

The activities of CSL's electronic engineers and computer scientists center in these principal areas: computer applications in a clinical environment, computer applications in laboratory research, and consultation with researchers in need of computer expertise.

CSL's method of approaching each project varies as each problem presents unique challenges. Sometimes the objectives of a project are clearly defined. The investigator knows exactly what he wants automation to achieve. In this case the path to solution of the problem is conceptually straightforward, even though it is often time-consuming and technically difficult. In projects of this kind, CSL staff analyze the user's specific requirements, evaluate various alternative solutions with regard to technical merit, time to completion, and cost. The hardware and software aspects of the system which best meet the user's needs are then specified.

A different approach is required when an investigator believes his research might benefit from automation but does not know exactly how to take advantage of the possibilities. In projects of this kind, members of CSL become more involved with the research in order to discover how automation can be achieved and how research methods need to be altered to utilize this technology.

When components that meet the user's needs are not commercially available, they are developed by the CSL engineering and programming staff. The system is refined to the point where it becomes a functioning, integrated part of the user's research. Since user's requirements often change as their research progresses, collaboration between the users and CSL staff continues beyond the initial implementation of the system so that necessary adaptations can be made.

Scope of Work

Over the past ten years, CSL has worked with nearly all of the Institutes on a wide variety of requirements. Major effort has been expended upon a few large projects that have required an investment of ten to twenty-five man-years. These projects, in addition to including initial analysis, design, development and installation phases, have frequently involved continuing collaboration with users in order to adapt systems to evolving research requirements. In fact, some of these projects have no distinct ending because of continuing modifications to accommodate new research protocols.

Each year, CSL also undertakes a number of relatively small jobs, ranging in size from one man-week to a half man-year. These involve consulting with the intramural and extramural programs in the areas of automated data collection, display and analysis, data transmission, certain aspects of biomedical sensor design and all aspects of real-time computer system design.

Intramural consultation often includes development of hardware and software systems; extramural consultation activities are primarily advisory. The consulting activities are valuable to us in that they help keep us aware of other activities in biomedical engineering, but require only a minimal commitment of manpower resources.

Highlights of the Year's Activities

During FY78, CSL has continued to utilize minicomputer and microcomputer based technology in support of clinical care and laboratory research programs of widely varying scope and duration. Three projects which reflect this diversity of effort and suggest the impact of CSL contributions to the biomedical community are the Computerized Radiotherapy Project, the NIAMMD Distributed Data Acquisition and Control Project and the Scintillation Counter Data Recorder Project.

The Computerized Radiotherapy Project is primarily concerned with the treatment planning aspects of radiation therapy. Treatment planning involves selection of the type, energy, size and orientation of therapy beams so as to insure adequate irradiation of the tumor volume, and requires accurate identification of the shape, size and depth of the tumor and surrounding normal radiation-sensitive tissue.

In the past, the methods available for acquiring such information have been relatively primitive as evidenced by the use of solder wire techniques for external contour determination, the estimation of internal cross-section contours from conventional linear radiographs, and the assignment of densities based upon representative values obtainable from atlases of cross-sectional anatomy.

Recent advances in ultrasound and computed tomography (CT) technology, however, have made it possible to differentiate between tissue that varies in attenuation characteristics by only 0.5 percent relative to water, thus providing a capability for attainment of accurate individual-specific internal and external contours. Moreover, the potential use of multiple slices suggests

that greater conformance of radiation dose to tumor volume can be achieved through the use of three-dimensional computation and display techniques.

The goal of early phases of the project has generally been to achieve improved patient care through the integration of ultrasound and CT developments into existing computer supported treatment planning technology. Emphasis is now directed toward the development of innovative border detection and display algorithms, and toward the exploration of sophisticated new treatment planning techniques (three-dimensional planning, optimization, dynamic control, etc.). This will facilitate the assimilation of evolving ultrasound and CT technology, and also provide a basis for in-depth assessment of the impact of this technology on radiation therapy.

The two and a half years that have elapsed since project inception have witnessed the development of a sophisticated stand-alone system that combines a powerful display facility with state-of-the-art treatment planning capabilities. Configured around a Digital Equipment Corporation PDP-11/70 computer, with 128K words of core memory and 40 million words of disc memory, the system maintains compatibility with EMI scans via 9-track magnetic tape, provides for scan display and manipulation on a 32-level of gray Princeton 801 display terminal, facilitates digitization of contours via an Atomic Energy of Canada Ltd. (AECL) Grafpen, and supports life-size reproduction of scans and selected contours on a Versatec printer/plotter. Treatment planning is accomplished using TP-11, a radiation treatment software package developed by J. R. Cunningham and marketed by AECL.

Within the context of a menu executive, programs have been developed that facilitate flexible interactive translation of EMI attenuation numbers to display intensity levels, permit manipulation of scan displays (sector selection, magnification, zooming, etc.), computer designated areas and distances, and provide automatic contouring for limited anatomic regions. Substantial current activity is concentrated on developing edge detection techniques and criteria adequate for organ and tumor identification. Convolution, probabilistic texture analysis, and line following techniques predicated upon "a priori" anatomic knowledge, are being evaluated both individually and collectively.

Additional on-going effort includes the development of a treatment planning optimization package utilizing linear programming techniques, and the integration of ultrasound images into the PDP-11/70 treatment planning system. Scheduled near-future activities include a number of modifications to TP-11 such as expanding the number of permissible contours so that inhomogeneity correction computations can fully utilize CT derived density data, software development for a color replacement to the Princeton 801 display terminal, and implementation of a data management system for tumor registry and scheduling purposes. In the more distant future it is planned to apply three dimensional display techniques to tumor volume determination and to resume study of dynamically controlled radiation therapy.

The Computerized Radiotherapy Project is a collaborative project involving radiotherapists and physicists of the NCI, and engineers, system programmers and application programmers of CSL. To date, CSL has invested 12 man-years of effort in the project. In as much as the project is comprised of a series of research tasks of unpredictable outcome and consequently uncertain medcal value, neither project duration nor the size of eventual manpower involvement can be confidently predicted at this time.

The Computerized Radiotherapy Project illustrates a minicomputer solution to a number of diverse but nevertheless centralized requirements. In contrast, the Distributed Data Acquisition and Control Project utilizes minicomputer and microprocessor technology to handle the data acquisition and processing requirements of several instruments distributed among various laboratories of the NIAMDD. Specifically, the Distributed Data Acquisition and Control Project is aimed at replacing an earlier Honeywell 516 computer system that has, for the past eight years, provided NIAMDD scientists with the ability to automatically collect data, display both raw data and computed values, implement feedback loops and perform a range of computations including area determination, smoothing, curve fitting, normalization of spectra, catenation of spectra, etc.

The existing and replacement systems enjoy similar goals but feature quite different technical approaches. An important difference that distinguishes the system under development is the use of a microcomputer at each instrument to perform all instrument-dependent functions and handle the real-time requirements. Data transfer from the distributed microcomputer to a centeral processor is accomplished through a communication microprocessor using standard communication protocols. A significant advantage of this system architecture is that the power of a shared central processor is retained while expensive specialized multi-user real-time system software development is exchanged for development of relatively simpler and lower cost microcomputer programs. Yet another benefit is that data acquisition, data storage, data transmission, and data processing capabilities can be readily upgraded, as required, through memory and peripheral expansion of the microcomputers. Finally, much of the software will be duplicated on each microcomputer thus providing for substantial standardization.

As in the case of the Computerized Radiotherapy Project, the Distributed Data Acquisition and Control Project is a large long-term project that consequently imposes heavy manpower demands. The staff assembled to perform the engineering design, equipment fabrication, system software development and applications programming required, although drawn primarily from CSL receives supplemental NIAMDD support. To date, CSL has expended approximately five manyears of effort on development of this system. Extrapolating from experience gained with the existing Honeywell 516 system, NIAMDD research programs can be expected to impose a continuing need for CSL to modify and expand the system thus precluding establishment of any firm date for project completion.

Expectations of system performance are high and it is anticipated that this distributed processing system will provide a model for automation of other NIH laboratories.

The Scintillation Counter Data Recorder Project is an excellent example of the significant role microprocessors and microcomputers have assumed in CSL development of laboratory instrumentation and data acquisition systems for the support of biomedical and clinical research. The relatively low-cost of microprocessor components and lower development effort which results from the use of microcomputers as compared to special-purpose logic enables us to undertake projects which previously would have exceeded our resources. More importantly, we have been able to significantly improve our turnaround time in responding to the requirements of investigators to the point that we can often react in periods measured in weeks rather than months. Specifically, the Scintillation Counter Data Recorder project involves the development of a microprocessor controlled instrument for logging data from liquid scintillation counters onto digital cassette tape. Scintillation counters are among the most widely used analytical instruments in biomedical research; there are approximately 300 of them at NIH. They are commonly used to detect and quantify radioactive tracers in biological specimens. The output device often supplied with a liquid scintillation counter is a teletypewriter or similar unit.

A typical experiment may require the analysis of hundreds of samples. This will produce large volumes of data which must be reduced and analyzed before the experimental results can be interpreted. Reduction of the data requires extremely tedious calculations, and is often done on a computer. In the past, this required that the listing from the teletype be manually transcribed or that a paper tape be read into a computer in some way. Either of these is almost as tedious as doing the calculations by hand.

The data recorder was developed with the thought of providing more convenient computer access to scintillation counter users, and improving reliability as compared to paper tape or manual transcription. The recorder produces an ANSI compatible digital cassette tape which can subsequently be replayed on any of a variety of commercially available terminals with cassette tape capability. Through use of a microprocessor as a control element, it has been possible to produce an instrument which can be easily adapted to a wide variety of scintillation counters with virtually no hardware changes. An additional benefit is the ability to perform some data editing and formatting functions within the data recorder so as to reduce the cost and time associated with data transmission. Finally, the microprocessor has allowed the per unit costs of these devices to be kept to a minimum due to reduction in parts count and development time.

In addition to system development, consultation to NIH intramural and extramural programs has recently been gaining significant prominence among CSL activities. The nature of this consultation ranges from brief encounters in

which engineering advice related to the selection of a particular piece of equipment or a computer technique is given to in-depth programmatic assessments. A typical example is our association with the Carcinogenesis Testing (CGT) Program of the National Cancer Institute. NCI has entered into an interagency agreement with the National Center for Toxicological Research (NCTR) of the Food and Drug Administration which will lead to the implementation of various aspects of NCTR's Research Support System as a computer-based information and data management system for CGT. CSL's role is to assist NCI in the evaluation of various specialized hardware and software components of this system. In addition, we are advising NCTR on the development of microcomputer-based, programmable data acquisition terminals for use both by NCI contractors and NCTR. A request for proposals for these terminals has resulted from our collaboration with NCTR; proposals are expected to be received from prospective vendors in late summer, 1978. At that time, CSL staff will participate with NCTR and NCI personnel in the evaluation of proposals and the selection of a contractor.

II. ANNOTATED PROJECT AND ACTIVITIES LIST

1. Clinical Research, Patient Care Projects

Computerized Radiation Therapy, NCI, RO: CSL, in collaboration with the Radiation Oncology Branch, NCI, has developed a computer system to utilize the detailed contour and density information available from computer assisted tomography to improve radiation treatment planning. Our system allows the radiotherapist to review scans of a tumor area at a video terminal, vary the gray-level spectrum to emphasize a particular structure, or zoom on an interesting feature. Contours, which may be computer derived or manually defined, are then processed by software algorithms procured from the Atomic Energy Commission Ltd. of Canada, to provide sophisticated individualized treatment plans. Current emphasis is on the development of suitable image enhancement and edge detection techniques necessary for accurate organ and tumor identification. A data management capability, which would include development of a tumor registry and management of scheduling activities, is also planned.

Cardiac Intensive Care Unit Patient Monitoring Computer System, NHLBI, SU: A real-time, on-line patient monitoring system was developed to serve the four bed postoperative recovery room of the NHLBI Surgery Branch. The system provides beat-to-beat analysis of the electrocardiogram and arterial pressure waveform, in addition to continuous monitoring of venous pressure, body temperature, urine output, and blood loss. Derived parameters are stored for 72 hours in a disc memory and real-time data retrieval is performed from either bedside or nurses station display terminals. Additional features include a five-minute electrocardiogram memory, the computation of cardiac output by the dye dilution technique, and the automated detection of common ventricular arrhythmias. Currently, the arrhythmia analysis programs are being modified to allow the monitoring of patients with cardiac pacemakers, and programs for the computation of cardiac output by the thermal dilution technique are being completed. Future plans call for the automated generation of alarms based on variations in monitored parameters, the the connection of the operating rooms to the computer system in order to allow vital sign monitoring during the operative procedure.

Medical Intensive Care Unit Patient Monitoring Computer System, CC, DCCM: A commercially developed computerized patient monitoring system is being procured for the newly authorized Medical Intensive Care Unit. This system will provide for the periodic data logging of vital signs from the nine bed care unit. Vascular catheterization facilities within the unit will also be automated to provide on-line collection of hemodynamic data as needed. Long-term data storage is provided by disc memories and on-line data retrieval is accomplished from numerous display terminals within the care unit. A mass spectrometer subsystem will be integrated into the commercial monitoring system in order to provide for the analysis of respiratory gases. In addition, urine scales will be added to each bed to allow the automated monitoring of

urine output and automated infusion pumps will eventually provide the capability for closed-loop therapy under computer control. Patient monitoring algorithms will be developed to allow the correlation of respiratory gas composition data and urine output values with vital signs obtained by the commercial monitoring system. New techniques for the automated evaluation and treatment of critically ill patients will be investigated. Programming modifications to the existing commercial patient monitoring system will ultimately customize the system to NIH applications.

Cardiac Scintillation Probe, NHLBI, IR CB, and CC, NM: CSL is continuing development of the microprocessor based cardiac scintillation probe. The purpose of this instrument is to allow continuous, noninvasive monitoring of left ventricular function. The microcomputer and electronics are mounted on a cart which can be easily positioned at the bedside. The system is programmed to automatically (1) acquire scintillation data from the probe, (2) organize the data into a composite left ventricular time-activity curve, (3) permit the curve to be constructed only from heartbeats having a user-selected range of lengths, (4) correct the curve for left ventricular background, (5) calculate ejection fraction, and (6) display the curve and all calculated values of ejection fraction as a function of time from the onset of monitoring. Clinical results, reported to the American Heart Association in November 1977, have demonstrated the utility of this system. We are currently working toward extending the capabilities of the system for use in the Cardiac Catheterization Laboratory to produce real-time pressure-volume curves in addition to monitoring LV volume. The system will be used there for drug intervention studies.

Cardiovascular Signal Analysis, NHLBI, IR SU: This project was terminated during the FY78.

S-T Segment Mapping, NHLBI, IR CB: Work on this project was suspended during FY78 and the status is therefore unchanged from the previous reporting period.

Automated ECG Processing, CC and NHLBI, IR CB: The Clinical Center's ECG Service requested assistance in specifying and acquiring an on-line ECG system to assist staff physicians in analyzing and reporting current ECG's and comparing serial ECG's. CSL has reviewed available literature, commercial systems, and DOD's Tri-Service Medical Information System procurement effort. A draft request for proposals containing functional specifications has been prepared for a minicomputer-based ECG system. The system is to perform the ECG analysis functions mentioned above and also have provision for further development, particularly with regard to integrating it with the Clinical Center's Medical Information System. The RFP is currently awaiting action by the appropriate Contracting Office; funding of the system is expected to be accomplished with the FY79 money.

2. Laboratory Investigation Projects

Flow Microfluorometry, Cell Sorter (FMF) NCI, I, LP and NIAID, LMI: The demand for FMF instruments has increased here at the NIH and in the research community at large during this reporting period. Here at the NIH, the demand for data collection and analysis exceeded the capability of the PDP-11/40 which was shared by both the FACS II FMF (Dr. Wunderlicht I, NCI) and the LASL FMF (Dr. Herman LP, NCI). A computer dedicated to each FMF was proposed by CSL, DCRT, and a major portion of the effort expended during this reporting period was aimed at providing an essentially identical dedicated system for each FMF. A PDP-11/34 was purchased and the existing dual system software was altered and optimized to support a single FMF instrument. Both FMF instruments now have dedicated computers and the emphasis has returned to improving existing and implementing new support software. Primarily, improvements to the software will considerably reduce the time spent by researchers at the computer console while using data display and analysis programs. This will be accomplished by allowing preselection of parameters that will automatically be applied to one or many data files without operator intervention. The capabilities provided under a new release of the operating system (RT-11 3-B) will be required to support the larger application programs and therefore existing programs will be adapted to run under it.

CSL has agreed to support a third system, FACS II PDP-11/34, requested by Drs. Asofsky and Chused of LMI, NIAID. All major items have been ordered for this system, and the FACS II/PDP-11 interface will be fabricated by a commercial vendor to specifications detailed in an RFP developed by this laboratory. Software (and hardware) developed for the existing systems have received wide acceptance and many copies have been sent to research groups not directly affiliated with NIH.

A requirement for the separation of cells based on more sophisticated combinations of the present measured cell parameters began a new aspect of CSL support for the FMF instruments. The crucial factor in any implementation of a more sophisticated separation scheme is the time required to make the sort decision after the FMF cell measurements are made. The direction in which to sort one cell must be determined before the next cell's arrival into the decision process. The temporal spacing of the cells in the FMF instrument affect the maximum decision time that can be taken for sorting. This time interval spacing between cells was thought to be some random distribution, but no published data was available to confirm this. A hardware, cell to cell, time interval measurement system was designed and fabricated by CSL and added to the FACS-II - PDP-11/40 system. With this addition, it was possible to quantify the distribution of the time intervals between cells for various average cell flow rates and then, project the number of cells that would be lost as a function of the average cell flow rate and a fixed decision time. Another use for this measurement is being explored within DCRT. Through statistical analysis of the time interval distributions of various types of cells and various types of cell preparations it may be possible to quantify some biological characteristics of the cells such as the cells' affinity for one another.

Distributed Data Acquisition and Control System, NIAMDD: A prototype Distributed Laboratory Data Acquisition and Control System is being implemented for NIAMDD, in Building 2, as an eventual replacement to the Laboratory Computer System developed here in CSL several years ago and which has now become overloaded. The new system will consist of a network of remote microprocessors connected in a star configuration through a communications microprocessor to the existing Honeywell 516 (H-516) computer. Laboratory data will be collected locally in real-time and transmitted at a convenient time to the communications processor using DDCMP, a standard communications protocol.

Significant progress occurred during the past reporting period, particularly in procuring and fabricating those links essential for the first laboratory node and link to the existing Honeywell 516. A prototype computer (LSI-11) chassis was fabricated with a larger back plane (6 X 9 slots) than available in commercial units. Five additional units based on the prototype were subsequently built under contract. Sufficient computer modules (central processing unit, memory, input/out) have been purchased for three functional computers and depot maintenance (1 spare of each module). The communication processor and its link to the H-516 are in place and software implementing the protocol for the transfer of files is being developed and tested for this link.

Display and menu routines have been programmed for the laboratory (LSI-11) computer. The effort involved in developing the hardware and software for the communication processor and much of the laboratory software such as display and menu routines are shared and will require minimal changes as other laboratory computers are added. An interface between the C-118 spectrophotometer and the laboratory computer has been designed and is being fabricated. Real-time data acquisition and control software is being developed to support the C-118. This interface and support software are dependent on the requirements of the C-118 and each new laboratory installation will have similar instrument dependent requirements. The technique to be used to implement the serial link between the communication processor and laboratory computer is being evaluated and a decision on the most time expedient route to implementing a subset of DDCMP (Digital Data Communications Message Protocol) will soon be made.

Mass Spectrometer, NIMH, LCS: This is a collaborative project with Dr. Markey NIMH, that is designed to automate ion focusing and data acquisition from an LKB 9000 mass spectrometer. Ion focusing is accomplished using a PDP-11/10 computer to control the accelerating voltage of the spectrometer. Although data acquisition and control are essential, the compelling reason for developing this system was to allow a user to create and use his own data manipulation routines, a feature not present on commercially available mass spectrometer data systems. During this reporting period, all hardware and software required for trained personnel to begin using the Selected Ion Recording System (SIRS) for chemical analysis in the laboratory environment was completed. An operations manual has been prepared to explain SIRS to laboratory personnel.

In April 78 the SIRS hardware was moved from the development area in Building 12A to Dr. Markey's lab in Building 10, Room 3N325. The system is in daily use, and we are adding improvements based on their laboratory experience.

Improvements already completed include; 1) a hardware addition to the Phoenix ADC/PDP-11 interface to reformat the ADC data directly into the computer's double precision integer format, freeing the CPU for more efficient real-time operation, 2) software enhancements to allow the automatic acquisition and processing of data from a series of samples without reinitialization between samples, 3) provision for a real-time display of acquired data during the acquisition process.

Considerable production time has been lost because of multiple failures in the LDK-9000 mass spectrometer. Preliminary versions of software and hardware developed for SIRS have been requested by and supplied to FMC Corp., Princeton, N.J., and Karolinska Institute, Huddinge, Sweden.

Scanning Electron Microscope (SEM), NIAMDD, LCP and NCI, LP: CSL participated with Dr. William Hagins (LCP NIAMDD) and Dr. William Banfield (LP, NCI) in specifying additions to an ETEC Autoscan SEM to permit its use for quantitative x-ray analysis of biological samples. The instrumentation requirement was to retain the SEM as a microscope with 200A resolution while providing the capability to analyze x-rays generated by the electron beam in the sample by both Energy-Dispersive (EDS) and Wavelength-Dispersive (WDS) Spectrometry simultaneously. Both EDS and WDS require a dedicated computer for acquisition and data processing and display.

There were several commercial systems available or under development that would satisfy the instrumentation requirement; the task was to identify the system that offered a cost-effective solution with good expectations for a successful technical integration with the existing SEM. CSL is preparing a recommendation for the EDS and WDS instruments, after several visits to sites using SEM's with these features and numerous inquiries to potential suppliers.

Microanalysis Facility, DRS, BEIB: BEIB is undertaking the establishment of a microanalysis facility which will conduct electron energy-loss spectrometry studies with investigators of several institutes at NIH and NIMH. These studies will involve computer acquisition and processing of spectral data, investigation of techniques for computer control of the electron microscope, and investigation of image processing and pattern recognition algorithms.

In February 1978, CSL's assistance in the computer system design, procurement, installation, and hardware and software development was requested. After discussions with the researchers involved with this project, CSL recommended the purchase of a PDP-11/60 computer system in May 1978, and initiated the purchase of such a system at a cost of $99,000, $40,000 to be contributed by NINCDS and the balance by CSL.

Delivery of this computer system and a Kevex Model 7000 Analytical Spectrometer is expected by October 1978. One of the first goals will be to interface this instrument to the computer system and adapt software to operate it.

Microcomputer-Based Satellite Controller, NIMH, LBEB: This year, we began the task of extending the capabilities of a laboratory computer system developed several years ago by the addition of a microcomputer satellite. The DEC LSI-11 microcomputer is being configured as a versatile programmable

multichannel pulse generator. The microcomputer will replace an existing system of manually controlled timers, wave-shapers, and pulse generators which control various aspects of evoked response experiments. Software running in the host PDP-11/40 computer will use information supplied by the user to compute parameters which determine the various timing relationships of the output pulses. At the time of execution, these parameters are transferred to the satellite where the microcomputer will generate the specified pulses on the chosen channels. In contrast to some of our other LSI-11 projects, the satellite requires no console, no operating system, and no auxiliary storage. Through this experiment we are expanding our host-satellite communication capabilities and are developing techniques for configuring and programming PROM-based DEC LSI-11 systems which should prove valuable in futur applications.

NIEHS Computer Facility, NIEHS: The Biometry Branch of NIEHS is responsible for providing computer facilities for the Institute. The data processing needs include scientific and statistical computation, simulation, and laboratory data processing. Since 1978, these needs have been met with a DEC GT-44 Computer System which was purchased and installed on the advice of CSL. CSL has since that time provided support in the form of technical advice and consultation services.

Faced with an anticipated further increase in demand placed upon their saturated system, the Biometry Branch requested CSL to make recommendations for expansion of their computer facility. In March 1978, CSL reviewed the current and anticipated future data processing requirements of the NIEHS and recommended 1) the purchase of a DEC PDP-11/70 computer system to augment the present GT-44 laboratory data processing system, and 2) investigation of methods to upgrade the telecommunications service to the DCRT Central Computer Facility.

Based on these recommendations, NIEHS is purchasing the suggested computer system. CSL has begun a survey of available telecommunication multiplexors and concentrators which might be used to improve telecommunications service, and plans to present the findings to NIEHS and CCB for possible implementation. CSL will also continue to provide support for the Biometry Branch computer system.

Pulsed NMR Spectroscope, NCI, DCT: The development of a microprocessor based acquisition and control system for use in conjunction with a Bruker Pulsed Nuclear Magnetic Resonance Spectrometer was started in early 1978. This unit, when completed, will replace the manual timing unit normally used with the spectrometer. The user will be able to pre-program a series of complex pulse sequences and have them generated under microprocessor control while experimental data is simultaneously acquired via an analog-to-digital converter. This method will not only relieve the experimenter of the tedium of setting a series of switches for each run but will also allow a new flexibility in the types of sequences that can be generated.

Bioassay Information System, NCI, DCCP, and FDA, NCTR: The National Cancer Institute has entered into an interagency agreement with the National Center for Toxicological Research which will lead to the implementation of various

aspects of NCTR's Research Support System as a computer-based information and data management system for NCI's Bioassay Program. CSL is serving as a consultant to NCI in evaluating various specialized hardware and software components of this system, and is providing consultation to NCTR on specifications for the development of microcomputer-based, programmable data acquisition terminals. A request for proposals for these terminals is complete; proposals are expected from prospective vendors in late summer, 1978. CSL will participate in the evaluation of proposals.

Laboratory of Immunology, NIAID: CSL is expanding the capability of a laboratory data acquisition system which we developed several years ago. The purpose is to accommodate increased use of the system by providing for the simultaneous acquisition, storage, and processing of instrument data from multiple instruments, as well as supporting interactive terminal processing. By September of 1978, the system will be completed, documented, and operational for use as described above for a Beckman amino acid analyzer, a Guilford spectrophotometer, and three fraction collectors. Provision is made to record the data on disk, annotate it with appropriate identifying information, analyze data from previous runs, and simultaneously and independently execute unrelated computer programs such that none of these functions will in any way affect or endanger the others. Provision has also been made for transmission of data to the DEC 10 for more sophisticated analysis. The transmission technique is described separately in this report as the Computer Communications (CLINK) project.

CSL Data Recorder (Previously reported as Scintillation Counter Data Logger): The CSL Data Recorder was designed for the unattended recording of data from liquid scintillation counters onto digital magnetic cassette tape. The recorder is connected between a scintillation counter and the counter's teletype, and in no way affects the operation of either the counter or its teletype. At the completion of an experiment, the tape may be removed from the recorder and played back to a computer for analysis using a commercially available cassette tape data terminal. Three Data Recorders, one for NIAID in Phoenix, Arizona, and two for NICHD in Building 10, have been successfully in use since mid-1977. Eighteen additional units are now being fabricated. These will be used in laboratories in NCI, NIDR, NICHD, and NIA, and should be installed and operational by late summer 1978.

Potentiometric Titration Controller, NHLBI, IR LC: A microprocessor-based system for measuring and controlling the electrical potential of an aqueous solution while monitoring optical density has been developed in conjunction with the Lab of Cell Biology (LCB), NHLBI. The degree of oxidation or reduction can be determined spectrophotometrically and controlled by pulses of electric current. The ability to control solution potential also allows complete optical spectra to be taken at fixed redox potentials. This past year, the system was used to study the respiratory chains of bacterial and mammalian systems. In particular, it was found that there are more redox components in E. Coli respiratory membranes than have been previously recognized. A new multi-channel spectrometer used in conjunction with the existing microcomputer will allow the investigator to take complete optical spectra in 2.5 milliseconds compared to the present time of 30 to 40 seconds, a factor considered of great significance due to the extreme volatility of the experimental conditions.

Intramural Laboratory Support: Support for intramural research laboratories through the development of specialized computer systems and data acquisition and control systems has long occupied a significant portion of CSL resources. The current year represents a continuation of this trend. Many projects in this category require the investment of substantial manpower and resources and are therefore reported separately. Those which can be accommodated by efforts ranging in duration from a few hours to a few weeks have not been reported as separate projects. A number of the tasks are illustrative of the variety of applications in which microcomputers may be used. Brief descriptions of a number of these projects are included.

A. Dr. C. B. Anfinson of NIAMD has requested that we develop a peak detecting device for use with a high pressure liquid chromatograph. The unit is to detect peaks, and, on the basis of that detection, control the advance of a fraction collector so that separated material from the chromatographic column may be collected. The problem is complicated by the fact that the peaks are incompletely separated and therefore often strongly overlap rather than returning to baseline. A microcomputer will be used for performing the arithmetic operations required by the slope detection algorithms used to solve this problem. Work on this project was begun in mid-June, 1978 with the expectation of completing it by late summer, 1978.

B. An interface designed for NIDR provides the investigator the capability to transmit data from a Nicolet VA-500B spectrum analyzer to a PDP-11/70 computer. The data is simultaneously recorded on cassette tape via a Texas Instruments 733 ASR terminal as a backup should the PDP-11/70 not be available. In addition to the data transfer capabilities, the interface provides high-speed (1200 baud) communications between the PDP-11/70 and the TI terminal. The CSL unit incorporates a commercially available single board microcomputer as well as circuitry and software developed by CSL. The unit has been in use since January 1978.

This microcomputer data recorder for NIDR will log data from a spectrophotometer onto cassette tape. The recorder will record from one to thirteen readings per specimen upon command from a front panel switch of the recorder. The recorder will also record control and status information which will be used when the cassette tape is played back to a PDP-11/70 computer. This project should be completed by September of 1978.

C. A microcomputer controlled data logger was designed and built for NICHD to replace an existing punched paper tape data acquisition unit. The recorder accepts an analog signal from a gel scanner, converts this signal to digital form, displays the digital data and records it on digital cassette tape. The analog signal can be sampled at ten different rates from 1 sample/second up to 10 samples/second. These and other characteristics of the device can be altered by simply revising the microprocessor program. This system has been in use since May 1978.

3. Program Management and Administration: No Projects

4. Biomedical Communications Project

Computers in Cardiology Conference: CSL has continued its support of the annual International Conference on Computers in Cardiology. The Conference provides a forum for direct interaction and exchange between physicians, computer scientists, and engineers who are involved in various aspects of clinical systems in the field of cardiology. CSL helped coordinate the 1977 Conference at the Thoraxcentrum, Rotterdam, The Netherlands, and edit the Conference Proceedings. We are also involved in the planning of the 1978 Conference which is to take place at Stanford University.

5. Computer Research and Technique Develoment

Computer Communications, DCRT, CCB: It is often necessary to be able to transfer information between laboratory minicomputers and a large computer system such as the DECsystem-10 in order to exploit the large system's data analysis and software development facilities. To meet this need, a software package called "CLINK" (Communications LINK) has been developed jointly by CSL and CCB. CLINK enables communications between DEC PDP-11's (the most commonly used minicomputer at NIH) and the DECsystem-10.

CLINK provides the following capabilities:

1. Terminals physically connected to a PDP-11 which is, in turn, connected to the DECsystem-10 can operate as "virtual terminals"; i.e., the terminal appears to be a normal terminal connected directly to the DECsystem-10 and can be used to perform all the usual time-sharing functions.

2. Data files can be transferred from the PDP-11 to the DECsystem-10.

3. Data files can be transferred from the DECsystem-10 to the PDP-11.

An experimental version of CLINK was implemented and extensively tested in FY77 The first production version (CLINK Version 2) was stabilized and made availabl for distribution in November 1977. CLINK was extended to run under RT-11 V3 S/J and F/B operating systems on the PDP-11 in January, 1978. The RSX-11M operating system version was extended to run under RSX-11D V6.2 by Lilly Research Laboratories; this software was made available to DCRT for distribution with the original CLINK software in May, 1978. Currently, CLINK is in operation on over 16 PDP-11 systems on campus and has been distributed to at least 40 sites outside NIH.

LEVEL OF EFFORT AND CAPITAL EXPENDITURE BY MAJOR PROJECT (July 1977 - September 1978)

Project Title	Project Leader	Effort (Man Years)	DCRT Capital Invested
Computerized Radiation Therapy, NCI, RO	Syed	4 1/2	30K
Cardiac Intensive Care Unit, NHLBI, SU	Syed	3 1/2	5K
Medical Intensive Care Unit, CC, DCCM	Syed	1 1/2	5K
Cardiac Scintillation Probe, NHLBI, IR CB, & CC, NM	Schultz	1 1/2	10K
Cardiovascular Signal Analysis, NHLBI, IR SU	Schultz	0	0K
S-T Segment Mapping, NHLBI, IR CB	Plexico	0	0K
Automated ECG Processing, CC and NHLBI, IR CB	Plexico	1/4	0K
Flow Microfluorometry, Cell Sorter, NCI, I, LP & NIAID, LMI	Schultz	2	20K
Distributed Data Acquisition & Control System, NIAMDD	Schultz	2 2/3	26K
Mass Spectrometer, NIMH, LCS	Schultz	1 2/3	4K
Scanning Electron Microscope, NIAMDD, LCP & NCI, LP	Schultz	1/3	0K
Microanalysis Facility, DRS, BEIB	Plexico	1/4	60K
Microcomputer Based Data Acquisition & Control	Plexico	2/3	5K
NIEHS Computer Facility	Plexico	1/6	0K
Pulsed NMR Spectroscopy, NCI, DCT	Plexico	1/2	4.5K
Bioassay Information System, NCI, DCCP & FDS, NCTR	Plexico	1/6	0K
Laboratory of Immunology, NIAID	Plexico	1	0K
CSL Data Recorder	Plexico	1 1/2	15K
Potentiometric Titration Controller, NHLBI, IR LC	Plexico	1/3	10K
Intramural Laboratory Support	Plexico	1/2	6K
Computers in Cardiology Conference	Ostrow	1/6	0K

III. Publications and Presentations List

Plexico, P., Songco, D., and Ostrow, H.: Microcomputers in Biomedical and Clinical Applications, National Bureau of Standards--IEEE Conference on Microcomputer Based Instrumentation, June 1978.

Miller, M., Powell, J., Sharrow, S., and Schultz, A., Jr.: Rapid Data Collection, Analysis and Graphics for Flow Microfluorometry Instrumentation. Review of Scientific Instruments, Bookhaven, National Laboratory, Upton, Long Island, N. Y., August 1978.

Ader, R., Lepley, A., and Songco, D.: Utilization of a Microprocessor in a Pulsed NMR Spectrometer. Journal of Magnetic Resonance 29, January 1978, pp. 105-111.

Hendler, R., Songco, D., and Clem, T.: Automated Electrodic Potentiometry System. Analytical Chemistry, Vol. 49, No. 13, November 1977, pp. 1908-1913.

Bacharach, S., Green M., Ostrow, H., Redwood, D., and Johnston, G.: ECG-Gated Scintillation Probe Measurement of Left Ventricular Function, Journal of Nuclear Medicine, Vol. 18, January 1977, pp. 79-84.

Bacharach, S., Green, M., Borer, J., Douglas, M., Ostrow, H., and Johnston, G.: Real-Time Scintigraphic Cineangiography. Presented: Computers in Cardiology Annual Meeting, October 1976, St. Louis, MO. Published in Proceedings. Available: IEEE Computer Society, Long Beach, CA 98403, IEEE Catalog No. 76CH1160-1C.

Bacharach, S., Green, M., Borer, J., Douglas, M., Ostrow, H., and Johnston, G.: A Real-Time System for Multi-image Cardiac Studies. Computer Methods, David E. Lieberman, Editor, Book Chapter, December 1977, C. V. Mosby Co., St. Louis MO.

Bacharach, S., Green, M., Borer, J., Douglas, M., Ostrow, H., and Johnston, G.: A Real-Time System for Multi-Image Gated Cardiac Studies. Journal of Nuclear Medicine, Vol. 18, January 1977, pp. 79-84.

October 1, 1977 through September 30, 1978

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT

2. Computer Center Branch

3. Joseph D. Naughton
Chief

I. SUMMARY

Function

The Computer Center Branch was established to provide efficient and effective central computational services for the NIH on a fee-for-service basis under the NIH Service and Supply Fund. The objective of the Computer Center is to incorporate proven advances in computer technology and methodology into a reliable, accessible, economic Computer Utility to support NIH scientific and managerial programs. The need to preserve the integrity of data and insure the uninterrupted availability of computer services is its primary concern. Its challenge is to achieve new improvements while maintaining the quality of service to science and its management at NIH.

The main concern of users of the Computer Utility is "How can I use the computer to better accomplish my job?" and once using the system, "How fast can I get results?" Continual additions or improvements are essential to maintain the responsiveness of the Utility and to provide services consistent with the rapidly changing state-of-the-art of computing.

Activities

The NIH Computer Center designs, implements, and operates a powerful network of modern computers and communication facilities. The nucleus is composed of two large multi-computer subsystems, the IBM System 370 and the DECsystem-10, each having unique capabilities. Communications facilities link these two subsystems and connect them by telephone lines to over 1,500 terminals of various types located in research laboratories and administrative offices throughout NIH. The computing and communications equipment (systems hardware) are controlled, balanced and complemented by a very complex set of computer programs (systems software) designed and implemented by the Center or acquired from other sources and adapted to meet the complex requirements of the NIH research program.

Services and facilities provided by the Center include standard programming languages (e.g., FORTRAN, COBOL, PL/I, SAIL, Assembly Language), a data base/data management system (IMS), and a large and varied library of utility programs. For users with terminals there are also interactive systems such as WYLBUR, TSO, and the time-sharing services of the DECsystem-10, which facilitate creation, submission and output of jobs and permit direct interactive computing (using FORTRAN, BASIC, CPS, APL, MLAB and other languages). The Center also provides a variety of facilities for the output of printed material or graphics information on paper and microfiche. Programs to show two or three dimensional pictures on cathode ray tube displays and "sketch pads" for advanced graphic projects such as those examining macro molecular structures are also available.

In addition, the Center provides extensive training, technical documentation, information services and assistance with problem diagnosis for its users throughout NIH. It also offers limited sources for data entry and recurring program maintenace and recurring production application.

Scope of Work

The Computer Center operates the NIH Computer Utility 24 hours a day providing services to over 6,000 users, including research scientists and program manager from all NIH Bureaus, Institutes, Divisions and Offices.

IBM System 370 Facility: During FY78, the workload handled by this facility grew 18% over the previous year. (Page 113 is a chart of workload growth since 1967.) At year's end, the Center was handling over 400,000 tasks per month. This number includes 9,600 mainstream jobs a day processed by the utility, with 80% of them completed within one hour. Interactive timesharing sessions via remote terminals have risen to over 4,500 a day.

DECsystem-10 Facility: The level of activity on the DECsystem-10 has shown steady growth over the past year. The number of user sessions now exceeds 12,000 per month, while the number of registered users has climbed to over 1,200. The number of connect hours has grown to over 12,500 per month while total runtime of the processors has remained steady at approximately 320 hours per month. Unfortunately, system response time has degraded noticeably due to the lack of sufficient CPU capacity for handling the workload.

Manpower: Only a small part (about 12%) of the operating expenses of the Computer Center are personnel costs, but those 142 people are the absolutely essential ingredient in the Center's success in providing cost effective

computing at NIH. About two thirds of them have responsibility at a daily operating level to insure that all work is completed in a timely and effective fashion within the Computer Utility. The remaining third are responsible for maintaining the integrity of the complex hardware and software systems, educating and assisting users in the use of the Utility and the design and implementation of new computer based services and facilities. While the overall workload of the Computer Center increased 18% in FY 1978, the number of people available to do the work remained essentially constant.

Highlights of this years activities

FY78 was the 11th consecutive year that the Computer Center provided NIH with planned improvements to existing services; added new facilities and reduced rates to users. Two major operating systems were upgraded, improvements were made in graphic services, printing and communication's facilities, and users received the benefit of rate reductions that totaled over 35%.

Upgrading of Systems

Communications Upgrade. The complete change to new high speed modems for all the interactive terminal systems, WYLBUR, TSO and the DEC10 represented a major improvement in the teleprocessing capabilities for the Utility. The conversion to the new modems involved eight months of close cooperation between the Computer Center, the telephone company and the users. The new modems operating at speeds of up to 1200 baud are the latest in communications technology. The modems combined with new Autospeed software, allows all users to dial the same number for a terminal system regardless of the speed and type of the particular terminal they are using. All ports on any interactive system operates in the same way and can handle the full range of terminals supported by the Computer Center. This improvement eliminated the inefficiency of the previous system which required segmentation of line groups to service each specific speed and terminal type. Over 600 modems were replaced at the Computer Utility without any interruption in service. Users modems were installed during a six week period. The entire conversion was completed in early July and is now in full-time productive use providing increased availability, higher reliability and greater efficiency for the total system.

Computer to Computer Communication link

Computer to computer communications became a reality during the year as CLINK, a program that allows many laboratory minicomputers to interchange information with the Central Computer Utility became a production service.

Files can be sent to or from the Central Facility to specialized laboratory computers throughout NIH. A powerful communications protocol insures that all of the transmitted data is received completely and accurately. CLINK also allows terminals connected to these laboratory computer to be used as ordinary terminals with either the DECsystem-10 or with WYLBUR and TSO, on the IBM System 370.

The CLINK system is a significant milestone in the support of scientific and laboratory computing. It recognizes the fact that specialized minicomputers and microprocessors can profitably team with the Central Utility's processor power and data storage facility to exploit the advantage of both.

New Surface Display System

The hardware for a high level display system was installed and special graphic system software was designed and implemented. Beginning October 1 this new facility will go into regular service providing graphic support for the modelling of macromolecular structure. The system provides highly interactive manipulation of molecular structure using a graphic tablet and pen. One form of modelling involves the manipulation of the structure to fit clouds of electron density which are derived from crystallographic data. The data bank developed for the AMSOM atlas can also be used as a source of macromolecular structure. An algorithm was developed for the representation of the Van der Waals surfaces of atoms as shaded and colored spheres. This algorithm makes it possible to display whole macromolecules or the active site for extremely large macromolecules. The system has been used to provide new insights into the structure of the active sites of serine proteases and the structure of collegen. The vector portion of the display system gives information about distances and angles between atoms as well as structural patterns while the surface representation display gives information about the packing of atoms. The results of modelling can be obtained from the system using a camera station which provides the possibility of instant filming, high quality plate filming as well as movie filming. Several movies on different macromolecular subjects are in production and planning. The system is being used by a broad population of biochemists and protein crystallographers who come to the system for working visits which last from a long day to a week. The system will be used in the next year to model the interaction between proteins and their substrates as well as to study the structure of the environment in which the proteins function. The possibility of doing these studies as well as the probability of success is largely determined by the hardware, algorithm and program development just finished.

Services and Facilities

DECsystem-10 Improvements. DECsystem-10 users benefitted from an increase in the speed of the mercury communication link, installed last year, which connects the DECsystem-10 and the System 370. The transmission speed of the link was increased from 4800 baud to 9600 baud. This link has proven so popular that an additional 9600 baud line was installed between the two sytems to avoid queueing problems at either end of the link.

APL users with Tektronix CRTs were able to utilize a new graphic capability, the APL-GRAPH-11 package. The high level interactive graphics language with English-like constructs was designed to make APL graphics functions readable and simple to use. APL's concise and easy manipulatoin of vector and matrix data makes it an ideal language for graphic applications.

Computer conferencing was introduced to the NIH community during the year. This experiment in teleprocessing allows many participants to record their views and feelings on a given topic. Conferees can also read the views of other and comment or argue for or against their points. The advantage of computer conferencing is that the participants do not have to gather at one place, at the same time. They can participate to whatever degree they wish and at the time which is most convenient for the individual.

A new digitizing system for inputing graphic data was offered to DECsystem-10 users. The system uses a CRT terminal with a graphics tablet to transform graphic data to a list of x and y coordinate values. This data can then be easily analyzed using MLAB or any other convenient data analysis program.

370 Improvements. A new Computer Output Microfilm (COM) device was installed at the Computer Center. The new DatagraphiX 4561 is 75% faster than the COM equipment that it replaced, and produces microfiche more efficiently and with improved readability. The primary advantages of microfiche over conventional printed output are thruput speed, rapid information retrieval, low cost, unlimited number of copies, and ease of handling, storage and distribution.

The installation of a second high speed printing subsystem enabled the Computer Center to offer users a new smaller standard size paper for printed output while improving operational efficiency. The old standard paper (14-7/8 x 11) was replaced with a new standard size of 11 x 8-1/2. The smaller print size permits the same amount of information (132 columns) to be printed on the smaller paper while maintaining readibility. The use of small paper provides an effective 20% increase in the print speed of

a 3800. Other paper size are still available to users through SPOUT and JES facilities. The improved system performance recognized from the transition to MVS last year permitted increasing the region size limit for all job classes to 1000K bytes and the elimination of class H. This change allows large programs to run in all job classes without resorting to the use of overlay structures or segmentation. The use of new large region size did not have any adverse impact on either turnaround time or system performance.

Terminal Improvements

After a three year interuption for procurement the Computer Center is again offering terminals to users. A new CRT, the NIH7000, has been selected and is being installed in laboratories and offices throughout NIH. The terminal features a customized keyboard, a larger buffer memory in which up to 200 lines may be stored, and numerous special features for use with NIH developed software systems. Twenty-eight lines of 80 characters are displayed with extremely sharp characters. The new terminal operates at 1200 baud and has a microprocessor controlling all the regular and special functions.

A procurement to select two types of printing terminals to replace the IBM model 2741 terminal which has served as the NIH standard for many years was also completed. New hardcopy terminals that operate at 1200 and 300 baud have been selected and will be available to users during the coming year.

Rate Reductions. Both the DECsystem-10 and the IBM System 370 offered rate reductions during the year. A DECsystem-10 reduction of 6% and an IBM System 370 reduction of 25% became effective in November for all users. DECsystem-10 users also realized savings of 28% when the rate for online disk storage was reduced to $.10 per block. System 370 batch service users benefited from a second reduction in May which ranged from 8% to 28% depending on CPU utilization. The constant tuning of the Computer Utility has provided cost reductions for the 11th consecutive year. As a result, users of the NIH Computer Utility again received more computing than they budgeted for.

User Education and Assistance

A crucial factor in the effectiveness of any Computer Center is the assistance it provides its users in learning how to use its facilities and services effectively and in overcoming any problems which they may encounter. For the tenth successive year the Computer Center offered a full program of Computer Training Courses and Seminars. Four, three month terms were offered for the first time this year. Audio visual and

computer assisted courses also made their debut during the year and were well received. Seventy-three courses provided training at all levels to over 1500 students this year. These courses covered the entire range of general purpose programming languages, special services and facilities, programming aides, job control languages, use of statistical and mathematical packages (BMD, SAS, SPSS, PSTAT, MLAB, MODELAIDE), query and reporting facilities (IRS), and programming tools (RMAG 21, PDP-11 tools). Seven seminars taught by DCRT mathematicians and scientists covered such diverse topics as computer netowrk synchronization, data structures and file organization, design of assemblers, curve fitting, simulation using GASP II, linear programming and Fourier and Laplace transforms. Unfortunately, some 650 applicants had to be denied admission to training courses because of the lack of personnel.

The Programming Assistance and Liaison (PAL) unit received more than 17,000 personal or telephone requests for assistance and analyzed some 3,400 written Programmer Trouble Reports (PTRs). Equally important, the Center helped its users avoid many problems through the publication and distribution of technical documentation. Its Technical Information Office used automated files to insure that all users received new or revised copies of technical manuals relative to their work. The Center celebrated the 10th anniversary of the publication of INTERFACE, its technical notes covering new services, facilities, procedures, diagnostics and programming hints in June. Seven issues containing some 400 pages of technical information for NIH computer users were published during the year.

Overall the Technical Information Office stocked and distributed some 70,000 pieces of documentation to over 3,600 active computer users, including technical reference manuals and guides and the Computer Center Users Guide. Both the Users Guide and the Timesharing Guide as well as many technical reference manuals were revised extensively throughout the year to keep abreast of changing technology and procedures.

Future Plans

Unfortunately, most of the activities which were identified as "future plans" in last year's report appear under the same title again this year. This lack of progress can be attributed to two primary causes; 1. Delays and burdens introduced by procurement procedures; and 2. Inadequate manpower to keep abreast of increasing workloads. As a result, the majority of the significant accomplishments planned for the past year appear again as "future plans."

The Center is still faced with severe shortages in several critical areas, online data storage space, physical space, data security, manpower, air conditioning and electrical power. Although contracts have been let to improve the physical plant to provide the necessary utility services and to improve security of the Computer Utility and the data it handles no real progress has been made.

As another year came to an end, the long awaited completion of Building 12B still remains a dream. If ever completed, the move of some of the Computer Center staff into it will enable the second floor of Building 12 to be converted into machine space if adequate housing can be found for the remaining staff. This will provide additional computer space to relocate the DECsystem-10 equipment currently in Building 12 and will enable all user-oriented facilities to be located together on the first floor of Building 12A. Locked user output boxes (similar to post office boxes) and a computerized access control system will be installed to provide better separation of the computer area from public areas and to protect personal data as required under the Privacy Act of 1974.

New WYLBUR, a completely redesigned version of the Center's most popular interactive system, is again planned for completion this year. Considering that it has already been delayed for the past two years there is the distinct possibility that it will actually happen this year. Most of the major parts have been completed and are currently undergoing extensive internal testing to insure a reliable service before it is offered as a standard service to NIH users. Considerable effort is currently being invested in the design of training courses and the preparation of extensive user documentation to insure a smooth transition to New WYLBUR when completed. The system will be available to users in the coming year providing them with more powerful editing commands, macro capabilities, document preparation facilities and many other new features which have been requested for many years.

As NIH research programs expand to include more and more research and patient care data and management information, data storage capacity continues to be the single more serious problem facing the Computer Center.

The tape library has overflowed its space many times over and online disk space is a constant problem. The future should see the introduction of a Mass Storage facility. Such a unit could store extemely large amounts of data in a relatively small space while reducing the manpower burden for computer operators and reducing overall storage costs. Data stored on a mass storage system is transferrable in a matter of seconds to online disk units where it is directly

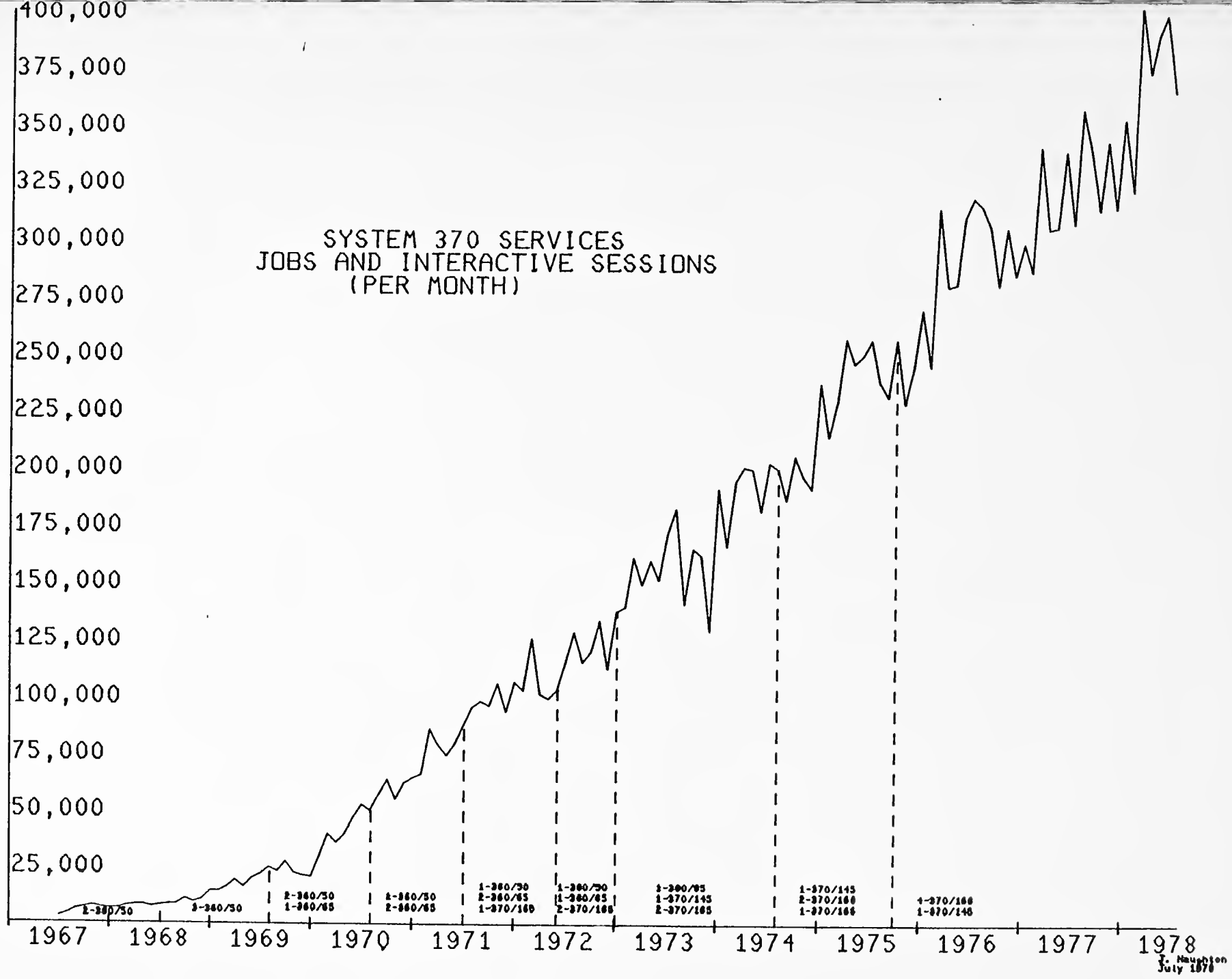
accessible by the main processors. A system study and sole source justification document for such a system was completed this year and will be forwarded to the GSA in early FY79. The only thing which can be assured at this time is that the request will be delayed and will require additional personnel effort to defend. Unless a mass storage facility is available in the immediate future, many NIH programs will suffer severely due to the unavailability of online storage space.

Plans to upgrade online disks have been well defined for the past two years but procurement regulations continue to delay installation. New units would enable the Center to increase its online storage capacity almost four-fold, provide a higher data transfer rate and provide improved reliability at no increase in operating cost. Because of more critical procurement issues, this activity has been suspended temporarily.

Recent industry improvements in computer system technology, together with new NIH program requirements for increased computational capacity/power and new functions, logically require that major components of the NIH Computer Utility be replaced by new, more cost effective units. In addition to new faster processors and disk drives with larger storage capacity for both the System 370 and the DECsystem-10 facilities, and a mass storage system, improvements are already long overdue for tape drives, communication controllers and batch remote job entry terminals of all types.

Unfortunately, constant contention with GSA over every improvement that NIH has identified in the past few years has prevented upgrading the present equipment to keep abreast of the needs of the NIH biomedical research program. The Computer Center is now forced by the GSA to undertake the largest single task it has ever attempted--the total competitive reprocurement of its entire complex (IBM and DEC) of hardware, software and maintenance service. This activity will consume the major portion of the professional staff of the Computer Center during the next year thus preventing much significant accomplishments in direct support of the NIH program. The cost in manpower, dollars and lost time and opportunity of preparing and conducting such a procurement(s) can not possibly be recovered regardless of the outcome.

The success of providing responsive, cost effective computer support in response to the complex and dynamic requirements of the NIH research program depends on fast straight forward procurement of the proper equipment at the right time. If the discussions with GSA of the past continue, it will be impossible to predict if or when the equipment necessary to provide proper support to the NIH biomedical research and management program will be available.


SYSTEM 370 SERVICES
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J. Naughton
July 1978

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00031-03 CC

PERIOD COVERED
October 1, 1977 - September 30, 1978

TITLE OF PROJECT (80 characters or less)

Atlas of Macromolecular Structure on Microfiche (AMSOM)

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Richard J. Feldmann, CCB, DCRT, Computer Specialist

Other: R. L. Tate, Ph.D., CSL, DCRT, Senior Staff Fellow

COOPERATING UNITS (if any)

Department of Chemistry, Brookhaven National Laboratory

LAB/BRANCH
Computer Center Branch

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bldg., 12A, Room 3009, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	.05	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Atlas of Macromolecular Structure On Microfiche (AMSOM) which was published in March of 1977 is being used by biochemists and crystallographers for teaching and research. Literature surveillance and structure validation is being done as preparation for a supplement to the atlas. A display system capable of representing the Van der Waals surface of a macromolecule in shaded colors has been implemented. Investigations are being carried out to determine the best media for the dissemination of this type of information. The current possibilities are stereo color microfiche using the already developed AMSOM vehicle as well as side by side stereo presentation on paper. Incremental dissemination using color xerography is being investigated as a way of avoiding the cost of color separation normally associated with printing.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00036-02 CCB

PERIOD COVERED

October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Graphic System for the Display of Biochemical and Biomedical Objects

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I. Richard J. Feldmann, CCB, DCRT, Computer Specialist

Others: Thomas K. Porter, CCB, DCRT, Computer Specialist
Charles R. T. Bacon, CCB, DCRT, Computer Specialist

COOPERATING UNITS (if any)

None

LAB/BRANCH

Computer Center Branch

SECTION

INSTITUTE AND LOCATION

DCRT, NIH, Bldg., 12A, Room 3009, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Implementation of graphics system for the representation and manipulation of biochemical and biomedical objects is being done at various levels of hardware, system software and user software. The communications link between the DECsystem-10 mainframe computer and the PDP-11/70 graphics computer was the focus of hardware and systems programming work. The operating characteristics of the link are being tuned to achieve maximum data transfer. The graphics system software which was obtained from the system vendor has been implemented and modified. System software for the frame buffer as well as general system infrastructure have been developed. An algorithm for the representation of atoms as shaded, colored spheres served as the starting point for the development of

high level user programs for manipulation of macromolecular structure. High level program development has centered about system supplied FORTRAN as no other language seemed to supply the needed operating characteristics.

A one micron densitometer is being added to the system to enhance the range of data which can be processed by the system.

The system has been used to manipulate data from nuclear scintograms.

October 1, 1977 through September 30, 1978

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT

2. LABORATORY OF APPLIED STUDIES

3. Eugene K. Harris
Chief

I. SUMMARY

Function

The Laboratory of Applied Studies (LAS) has three main purposes:

. in collaboration with biomedical scientists, to apply mathematical theory and computing science to the construction, testing and improvement of mathematical models of physiological processes, particularly dynamic flow processes, transport of substrate to tissues and macromolecular interactions;

. in collaboration with clinicians, to develop and apply mathematical or statistical theory and computer programming to improve diagnosis of disease and assessment of treatment;

. to engage in independent research in applied mathematics, statistics and computer systems necessary to provide a sound theoretical basis for collaborative studies.

LAS consists of two sections in addition to the Chief's office: 1) Applied Mathematics Section (J. E. Fletcher, Ph.D., Chief), including specialists in applied mathematics, numerical analysis, computer science, mathematical physiology; 2) Medical Applications Section (J. J. Bailey, M.D., Chief), including physicians, electronic (biomedical) engineers, computer systems analysts. The Chief, LAS, is a biostatistician.

Scope of Work

The Laboratory of Applied Studies works on projects in basic and clinical biomedical science. In large part these are carried out in collaboration with other groups at NIH and elsewhere in the U.S. and abroad. The collaborating investigators this year included:

. biochemists and pharmacologists - at U. of Iowa, Northwestern University, and other universities, working on models for receptors of drugs or other ligands, and the kinetics of enzymes in membranes.

- physiologists and chemical engineers - in the U.S., U.K., Scandinavia, and Germany studying the transport of substrate within the microcirculation,

- clinicians - at NIH in the cardiology and pulmonary branches of NHLBI,

- clinical chemists and pathologists - at NIH (Clin. Path. Dept., CC), in California, elsewhere in the U.S., and in the U.K., engaged in the collection of and study of reference values in laboratory medicine,

- electrocardiologists, biomedical engineers, and health administrators - in the U.S., Canada and Europe concerned with the evaluation of computer-based ECG interpretation.

During FY 78 LAS staff members participated in various teaching and consulting (or advisory) activities:

J. Fletcher continues to serve as Chairman of the Mathematics Department, FAES, and taught advanced calculus in the NIH graduate school;

J. Bailey was a member of several site-visiting teams for NHLBI concerned with computer analysis of exercise ECG's, biophysical studies in pediatric cardiology and studies in cardiovascular pathology;

E. Harris continues to be a consultant in applied statistics to the Food and Drug Administration's Division of Medical Devices and Diagnostic Products. Dr. Harris has also served as an invited speaker at meetings of American and European pathologists concerned with applications of statistical theory to problems facing clinical laboratories.

Highlights of LAS Program Activities during FY 78

1. Hardware analog model implemented on MAC-16 to simulate cone cell responses: E. Pottala, R. Covacci (LAS), S. Vallerga, R. Normann (Lab. of Neurophysiology, NINCDS): The most satisfactory mathematical model currently available to describe retinal cone cell activity is the Baylor-Hodgkin-Lamb model involving several nonlinear differential equations to describe sodium-potassium fluxes. Such models are too time-consuming and expensive for routine use on a digital computer; however, the analog hardware representation enables extremely rapid, inexpensive simulation of cone cell response to a wide range of graded light stimuli, including estimation of parameters and graphic display of response curve. It is hoped that this model system will be expanded to include a small network of cone, rod and other cells involved in the retina's processing of light stimuli.

2. Extracting accurate, precise estimates of ventilation parameters from radioxenon scintigrams of the lung: B. Bunow, B. Line, M. Horton (LAS), G. Weiss (PSL): Extensive computer simulation, paralleled by mathematical analysis, has developed previously unavailable information on the precision and accuracy of various methods of estimating washin-washout rates of radionuclide exchange from scintigraphic studies of lung ventilation using radioxenon. These results have not only quantified the cumulative effects of random variation in counting statistics but have also tested quantitatively the effects of different isotopes of xenon and the benefits of increasing dosage over shorter time periods, and have allowed a rational decision on the most suitable scintigraphic area to represent a lung compartment.

3. Role of myoglobin in facilitating the diffusion of oxygen in muscle: J. Fletcher, M. Bieterman (LAS): The Krogh capillary-tissue model and associated nonlinear oxygen-hemoglobin dissociation have been used to study the role of myoglobin in facilitating diffusion of oxygen in muscle. Taking blood flow rate into account, the resulting mathematical model has required development of new numerical methods of solution, particularly at boundary layer regions near the supplying capillaries. Preliminary results indicate that facilitation of diffusion through binding proteins such as myoglobin can be important at low flow or high tissue metabolic rates.

II. Annotated list of LAS projects

Mathematical modeling of biological processes: J. Fletcher (LAS), A. Spector (University of Iowa): Development and application of mathematical models and numerical methods in studies of substrate transport in the microcirculation, diffusion processes in physiology, and macromolecule-ligand binding equilibria.

Simulation of physiological systems: E. Hill, J. Fletcher, E. Harris (LAS); B. McLees (CC): Exploration and testing of computer programs simulating responses of physiological systems to determine the usefulness of such programs as consultants or quality control mechanisms in patient care.

Mechanisms of active transport; biochemical kinetics: B. Bunow (LAS); J. Rinzel (NIAMDD); J. De Simone et al. (Medical College of Virginia): experimental and mathematical studies of the energy mechanisms for active transport, and of multi-state biochemical kinetics in cells and membranes.

General mathematical and computational methods: E. Hill (LAS); R. Shrager (LSMM): Study of methods of fitting non-linear models utilizing other than least squares criteria. Evaluating methods of organizing large data files for rapid storage and retrieval.

Computer aided analysis of electrocardiograms: J. Bailey, M. Horton (LAS): Separate studies, conducted in collaboration with the Cardiology Branch, NHLBI, and a cardiologist in Glasgow, Scotland, to evaluate the utility of leading computer programs for ECG interpretation. Both studies include clinical documentation.

Computer-based modeling of pulmonary gas exchange: Many LAS staff members; staff of Diagnostic Imaging, (CC), and Pulmonary laboratory (NHLBI). Utilizing scintigraphic and other clinical data on lung function to construct sound mathematical and computer-based models of ventilation and perfusion in the lung.

Computer systems for diagnostic imaging: J. Bailey, M. Douglas, B. Line (LAS); H. Ostrow (CSL); M. Green and others (Diagnostic Imaging, CC): Development and application of computer systems to such diagnostic imaging activities as ECG-gated radionuclide angiocardiography, functional mapping and other scintigraphic studies of kidney, brain, heart and lung.

Hybrid computing to analyze physiologic signals and construct simulation models: E. Pottala, R. Covacci (LAS), S. Vallerga (Lab. Neurophys., NINCDS): Using LAS minicomputer system (MAC-16) for hardware simulation of physiologic functions (e.g., retinal cell activity) and analysis of analog signals (myogram, ultrasonogram, etc.)

Statistical research in clinical pathology: E. Harris (LAS), G. Shakarji (DMB); clinical chemists in California, U.K.: Application of variance component and time series analysis to description of reference distributions of clinical laboratory tests, to serial studies of normal biochemistries, and to the design of criteria for recommended precision and accuracy of analytic methods.

III. Publications

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Spector, A.A. and Fletcher, J.E.: Transport of Fatty Acid in the Circulation. In Dietschy, J.M., Dietschy, J.A., Ontko, J.A., and Gotto, A.M. (Eds.): The Physiology of Lipids and Lipoproteins in Health and in Disease. Bethesda, MD., American Physiological Society, 1978, pp. 229-249.

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Vallieres, B.J., Johnston, G.S., Jones, A.E., and Line, B.R.: Scintigraphy with gallium-67 citrate. I. Metabolism. Tome 106: 1275-1281, 1977.

Vallieres, B.J., Johnston, G.S., Jones, A.E., and Line, B.R.: Scintigraphy with gallium-67 citrate. II. Clinical aspects. Tome 106: 1382-1391, 1977.

van Rijk, P.P., de Graaf, C.N., Jambroes, G., Bacharach, S.L., Green, M.V., Line, B.R., and Bailey, J.J.: Functional imaging in nuclear cardiac studies. Computers in Cardiology. IEEE Catalog No. 77CH2154-2C, IEEE Computer Society, Long Beach, Ca., 90803, 1978, pp. 9-17.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00033-02 LAS

PERIOD COVERED

October 1 1977 to September 30 1978

TITLE OF PROJECT (80 characters or less)

Analysis of Coupled Transport and Biochemical Kinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	B. Bunow	Senior Staff Fellow	LAS	DCRT
OTHERS:	J. Vernevez	Prof. Univ. of Tech. Compiegne, France		
	J. DeSimone	Prof. Univ. of Va. (Medical College)		
	D. Mikulecky	Prof. Univ. of Va. (Medical College)		
	G. Weiss	Chief	PSL	DCRT
	J. Rinzel	Mathematician		NIAMDD
	R. Miller	Staff Fellow		NIAMDD

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Applied Studies

SECTION

Applied Mathematics Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, Md. 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project investigates two fundamental problems in biology: (1) role of dynamic patterns in embryological and evolutionary biology and (2) kinetics of enzymes located in cell membranes. The first area involves a demonstration of the role which simultaneous reaction and diffusion might play in the formation of biological patterns such as those which determine the shape of organs. The second area involves investigation of the effect of diffusion limitation by cell membranes on the kinetics of enzymes contained in them. Digital computer simulation and bifurcation theory are the principal tools of these investigation.

(1) Dynamic Patterns

Background and Objectives:

The objectives of this investigation are twofold. The first is a study of dynamic patterns in reaction-diffusion systems obeying realistic biochemical kinetics. The objective here is to demonstrate the structure of solutions to the descriptive equations of these systems which develop spontaneously when unstructured solutions are perturbed. The solutions obtained with the mathematical model are to be compared with results obtained in the laboratory with a working model. The adequacy of reaction diffusion models for explaining certain aspects of embryological pattern formation needs further clarification. For example, it is important to know the modification to be expected in the patterns when the size of the system is altered or the rate of enzymatic activity, as might occur due to mutations or change of temperature.

Significance to Biomedical Research:

Patterns generated by reaction-diffusion processes have been implicated in embryological organogenesis. There are a number of unanswered questions in this area which we address. 1) Are the patterns generated by reaction-diffusion sufficiently varied as to be capable of producing the many shapes seen in embryonic development? 2) Is the relation between the pattern obtained and the underlying reaction scheme sufficiently close that we might infer the latter from the former? Do the patterns succeed one another in a consistent way as parameters are changed, as would occur during growth?

Progress in FY 78:

It has been shown that a large number of different patterns can be obtained with a single reaction mechanism. Most of this variety can be explained without any detailed knowledge of the details of the reaction mechanism. Many different patterns can exist for the same values of all parameters in the mathematical model. In order for a reaction-diffusion mechanism to be operative in embryological processes, it is necessary that an additional mechanism be present to select among the possible patterns. The patterns show no unique succession with growth. These results suggest that the role of reaction-diffusion patterns in embryology is likely to be more complicated than has been recently speculated. A manuscript summarizing accomplishments during FY 77 has been completed and will be submitted shortly. Results from FY 78 have been presented internally and a manuscript is approaching completion.

(2) Kinetics of Enzymes

Background and Objectives:

A second direction of investigation is the effect of cell membranes

and surface structures on the kinetics of membrane associated enzymes. These enzymes are important in membrane transport, metabolic energy transduction, and intercellular communication. The goal here is to discover means of analyzing kinetic data from membrane-associated enzymes which permit correct conclusions about kinetic constants and mechanism.

Significance to Biomedical Research:

The design of pharmacological agents with which to modify the function of membrane-associated enzymes requires correct estimates of interaction between the enzyme and the agent. Only by taking the effect of the membrane into account can such estimates be obtained for enzymes in membranes. A kinetic analysis appropriate only to enzymes in solution has been widely misused in studies of enzymes in membranes. It is likely that many conclusions regarding the mechanism of such enzymes as well as the strength of their interactions with substrates have been incorrectly estimated in this way.

Progress in FY 78:

An analysis has been developed which permits correct determination of the affinity constants between membrane-associated enzymes and their substrates, products and specific inhibitors. Distinction between different reaction mechanisms is possible for these enzymes, but the patterns which they produce in conventional studies of mechanism are quite different from what is expected for enzymes in solution. In particular, membrane-associated enzymes typically appear to be cooperative due to the effect of the membrane. Application has been to the pharmacology of a sympatholytic inhibitor of acetylcholinesterase and to the kinetics of tripeptide transport in E. coli. A manuscript reporting on this work has been submitted for publication.

Proposed Future Course of Investigation:

Future efforts in the dynamic patterns area will involve consolidation of theoretical and experimental procedures. Work in the enzyme kinetics area will be elaborated to consider more complicated kinetic schemes specifically appropriate to membrane transport and metabolic processes.

Publications:

1. Bunow, B.: Chemical reactions and membranes: a macroscopic basis for facilitated transport, chemiosmosis, and active transport, part I. J. Theor. Biol., 1978 (in press).

2. Bunow, B.: Chemical reactions and membranes: a macroscopic basis for Active Transport, Part II. J. Theor. Biol., 1978 (in press).

3. Bunow, B.: Kinetics of membrane-associated enzymes: effect of transport limitation by boundary layers and membrane structure. (Submitted to Biochemistry, 1978).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00002-08 LAS

PERIOD COVERED
October 1, 1977 to September 30, 1978.

TITLE OF PROJECT (80 characters or less)
Computer Aided Analysis of Electrocardiograms

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Bailey	Chief, Med. Appl. Section	LAS	DCRT
	M.R. Horton	Computer Systems Analyst	LAS	DCRT
	J. Gottdiener	Chief, ECG Laboratory	CB	NHLBI

COOPERATING UNITS (if any)

P. Lawrence, Cardiology Dept., Walter Reed Army Medical Center
P. MacFarlane, Medical Cardiology, Glasgow Royal Infirmary, Scotland

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	1.2	0.1

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

These studies continuing since 1970 have been directed toward the evaluation of accuracy, clinical utility, and cost effectiveness of various computer systems for analysis of routine electrocardiograms (ECG's).

Background and Objectives:

In the past fifteen years numerous computer programs implemented upon a variety of computer systems have been developed for analysis of routine ECG's. Computer processing of ECG's has become a sizeable enterprise in many parts of the country, including both commercial bureaus offering service for a fee and non-commercial (academic or government) centers establishing the capability for themselves.

Since 1970, LAS in collaboration with the Cardiology Branch (CB), NHLBI has studied various programs to determine which, if any, would be useful to implement on the NIH campus. As a result of this work, an evaluation methodology was evolved which was published in 1974 and has become one of the standard references in the field. Although a program was selected and implemented in 1974 for daily use at NIH, additional programs and other computer systems continue to be evaluated as possible improvements to the NIH system with regard to cost and accuracy. Past evaluations have included the ECAN-D program (1964), the Mayo-IBM program (1968), the experimental IBM program (1971), and the AVA 3.4 (Pipberger) program (1975).

Progress during FY 78:

A series of 300 ECG's were collected on patients in the Glasgow Royal Infirmary, (GRI), Scotland. Clinical documentation of the patient's cardiovascular status by non ECG means in the form of enzyme studies, cardiac catheter laboratory data, etc. was obtained whenever such investigations were warranted, i.e. in most cases. The standard 12 lead ECG data was analyzed by the IBM program at NIH; modified McFee lead (XYZ) ECG data was analyzed by a program developed at GRI. The results of these two programs are being compared with respect to accuracy where clinical documentation exists and with respect to cardiologist agreement in all other cases.

A series of 110 ECG's were collected by CB, NHLBI on patients with a variety of conditions including hypertension, valvular disease, and coronary disease. In all cases, the size of the left ventricle has been estimated from ultrasound measurements of the septal wall thickness, posterior wall thickness, and internal end-diastolic diameter. The IBM program uses ECG features to compute points toward a diagnosis of left ventricular hypertrophy (LVH) in a manner somewhat similar to the Romhilt-Estes point score. The AVA 3.4 (Pipberger) program uses Frank lead (XYZ) ECG features to compute probabilities for LVH. The results of these two computerized LVH algorithms are being correlated with ultrasound measurements of left ventricular mass.

A method, published in 1974, for using interleaved digital samplings from the same analog tracing to test reproducibility of programs has been extended and applied to the ECAN-E program (1975) and Version 2 of the IBM program (1976). Guidelines for evaluation of ECG programs which were developed by LAS have been adopted by the American College of Cardiology (ref. 1).

Several manuscripts describing the above work are in preparation and one will be the subject of an invited paper at the 5th International Congress of Electrocardiology in Scotland.

Members of LAS and CSL developed specifications for a minicomputer system to be dedicated to ECG analysis which the Clinical Center plans to procure.

Significance:

The estimated number of computer-processed ECG's in North America in 1971 was 600,000; in 1972, it was one million; and in 1974 it was 4 million. In view of this exponential increase in computer usage, it will become ever more important to have methodologies and guidelines by which ECG computer systems can be evaluated.

These studies seek to establish the diagnostic limits of ECG itself and the degree to which computerized algorithms may achieve these limits. Important evaluation methodology continues to be developed, which may have a significant impact on the further diffusion of computer technology in electrocardiography.

Proposed Course:

The testing of these programs with clinically documented data, i.e., cases with correlative data from cardiac catheter laboratory studies, echocardiography, or scintigraphic studies, is expected to be completed within FY 79.

Publications and Abstracts:

1. Rautaharju, P.M., Ariet, M., Pryor, T.A., Arzbaecher, R.C., Bailey, J.J., Bonner, R., Goetowski, C.R., Hooper, J.K., Klein, V., Millar, C.K., Milliken, J.A., Mortara, D.W., Pipberger, H.V., Pordy, L., Sandberg, R.L., Simmons, R.L., and Wolf, H.K.: Report of Task Force III: Computers in diagnostic electrocardiography. In Proceedings of the 10th Bethesda Conference: Optimal Electrocardiography. Am. J. Cardiol. 41: 158-169, January 1978.

2. Bailey, J.J., Horton, M.R.: Reproducibility of Version 2 of the IBM Program with and without the Serial Comparison Option. The Fifth International Congress of Electrocardiology, 1978 (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 Ct 00034-02 LAS

PERIOD COVERED
Oct. 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Computer-based Modeling of Pulmonary Gas Exchange and Respiratory Mechanics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Bailey	Chief Medical Appl. Section	LAS	DCRT
	B.J. Bunow	Senior Staff Fellow	LAS	DCRT
	J.E. Fletcher	Chief, Applied Math Section	LAS	DCRT
	B.R. Line	Senior Assistant Surgeon	LAS	DCRT
	R.G. Crystal	Chief, Pulmonary Branch	PB	NHLBI
OTHERS:	E.K. Harris	Chief, LAS	LAS	DCRT
	M.R. Horton	Computer Systems Analyst	LAS	DCRT
	T.B. Stibolt, Jr.	Senior Staff Fellow	LAS	DCRT
	A.E. Jones	Asst. Chief	DI	CC
	J.D. Fulmer	Chief	PB	NHLBI
	B.D. McLees	Ch, Medical Intensive Care Unit		CC
	A.R. Mitz	Engineer	LAS	DCRT

COOPERATING UNITS (if any)

Diagnostic Imaging Branch	CC
Pulmonary Branch	NHLBI

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section, Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves a collaborative effort of LAS with the Diagnostic Imaging Department, CC, the Pulmonary Branch, NHLBI, and the Medical Intensive Care Unit, CC. It is directed toward a deeper understanding of pulmonary pathophysiology through the construction of computer-based models of pulmonary gas exchange and respiratory mechanics and comparisons of model predictions with real patient data.

PHS-6040
(Rev. 10-76)

Background and Objectives:

Numerous attempts have been made in the past to quantify pulmonary function. Inhomogeneities in the lung required certain simplifying assumptions to be made which tended to obscure the true nature of lung function. Furthermore, certain nonlinearities inherent in the lung system allowed only partial quantitative models and sometimes these could only be expressed in the form of nomograms or graphs.

Within recent years this has been changed by the advent of the digital computer and also by newer diagnostic tools, viz: pulmonary scintillation, cardiac catheterization, multiple inert tracer gas analysis and dynamic compliance studies.

This program involves the Pulmonary Branch, NHLBI; the Diagnostic Imaging Department, CC; the Medical Intensive Care Unit, CC; and the Laboratory of Applied Studies, DCRT. The objective is to construct computer-based models of pulmonary gas exchange and repiratory mechanics founded upon sound physiological considerations and descriptive mathematical formulations.

Progress during FY 77:

A computer simulation model was developed to test the accuracy and precision of various methods for extracting ventilation parameters from radioxenon studies of the lung. The simulation model showed how the results are affected by variations due to counting statistics and revealed how much improvement could be obtained through the use of a better isotope (xenon 127 instead of xenon 133), by increased dosage over a shorter time, and by using more pixels to represent a lung compartment (ref. 7).

The Kelman procedure which relates gas tensions and contents in blood for given values of hemoglobin, hematocrit, pH, etc. has been revised to incorporate Adair binding constants for hemoglobin, to remove unnecessary corrections in the formulae and also sources of numerical imprecision, and to utilize more efficient computer algorithms. A modification of the Kelman routine was used to determine regional gas contents from ventilation-perfusion scans of the lung (ref. 1).

A method for studying the distribution of inhaled radioxenon at different lung volumes has been devised. (ref. 2). With this method the effect of gross movement upon the extraction of respiration parameters can be studied. A method using radiogallium citrate to tag white cells was used to study active inflammatory processes in the lung and to correlate regions of inflammation with regions of ventilation-perfusion abnormalities (refs. 3-5).

Significance:

These computer-based models when combined with data from scintillation, cardiac catheter, and pulmonary laboratory studies should

allow a quantitative description of pulmonary pathophysiology on a regional basis. They should allow separation of diseases (e.g. bronchitis from emphysema), separation of disease components (obstructive vs. restrictive vs. vascular), assessment of severity of disease component, and prediction of the degree to which each component compromises overall pulmonary function.

Proposed Course:

The sources of greatest variation and potential error in estimating ventilatory parameters for xenon scintigraphy relate to counting statistics (Poisson noise), masking errors, gross respiratory movement, and variable background. These sources can be minimized through the implementation of: controlled patient breathing; reduced re-breathing reservoirs for radioxenon; hardware markers for end of washin/beginning of washout; and new software algorithms for masking and background subtraction.

The Kelman procedure (NIH version) will be validated with real data from the Clinical Center. So far as is known such validation has not been done before.

Publications and Abstracts:

1. Line, B.R., Dayhoff, R.E., and Bailey, J.J.: An algorithm for the production of regional gas partial pressures and blood contents from scintigraphic and physiologic data using an alveolar gas exchange model. In Howard, B.Y. (Ed.): Proceedings of Seventh Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine, Computer Assisted Data Processing. ERDA CONF-770101, 1977, 7: pp. 196-206.

2. Kushner, T.R., Line, B.R., Bacharach, S.L., and Johnston, G.S.: A spirometric method for gating xenon ventilation studies. In Howard, B.Y. (Ed.): Proceedings of Seventh Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine, Computer Assisted Data Processing. ERDA CONF-770101, 1977, 7: pp. 207-215.

3. Vallieres, B.J., Johnston, G.S., Jones, A.E., and Line, B.R.: Scintigraphy with gallium-67 citrate. I. metabolism. Tome 106: 1275-1281, 1977.

4. Vallieres, B.J., Johnston, G.S., Jones, A.E., and Line, B.R.: Scintigraphy with gallium-67 citrate. II. clinical aspects. Tome 106: 1382-1391, 1977.

5. Brereton, H.D., Line, B.R., Londer, H.N., O'Donnell, J.F., Kent, C.H., and Johnson, R.E.: Gallium scans for staging small cell lung cancer. JAMA, 1978 (in press).

6. Line, B.R., Fulmer, J.D., Reynolds. H.Y., Roverts, W.C., Jones, A.E., Harris, E.K., and Crystal, R.G.: Gallium-67 citrate scanning in the staging of idiopathic pulmonary fibrosis: correlation with physiology, morphology and bronchoalveolar lavage. Amer. Rev. Resp. Dis., 1978 (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00003-07 LAS

PERIOD COVERED
October 1, 1978 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Computer Systems for Diagnostic Imaging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.J. Bailey	Chief Med. Appl. Sec.	LAS	DCRT
	M.V. Green	Ch, Appl. Physics Sec.	DI	CC
	B.R. Line	Senior Assistant Surgeon	LAS	DCRT
OTHERS:	M.A. Douglas	Computer Systems Analyst	LAS	DCRT
	M.R. Horton	Computer Systems Analyst	LAS	DCRT
	E.W. Pottala	Engineer	LAS	DCRT
	S.L. Bacharach	Physicist	DI	CC
	T.B. Stibolt, Jr.	Senior Staff Fellow	LAS	DCRT
	P.R. Bradley-Moore	Staff Fellow	DI	CC
	R.G. Dunham	Computer Specialist	DI	CC
	G.S. Johnston	Chief	DI	CC
	H.G. Ostrow	Engineer	CSL	DCRT

COOPERATING UNITS (if any)
Diagnostic Imaging Department, CC, NIH
Computer Systems Laboratory, DCRT, NIH

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.1	3.0	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project involves computer-based mathematical analysis, pattern recognition, and image processing in support of diagnostic activities in the Diagnostic Imaging Department of the Clinical Center and collaborating Institutes. Applications include computerized ECG-gated radionuclide angiocardiography and scintigraphic studies of regional cerebral blood flow, renal dynamics, gastric fluid dynamics, and pulmonary ventilation-perfusion relationships as well as computer analysis of ultrasonograms.

Background and Objectives:

Since FY 72 LAS with engineering support from CSL, DCRT and in collaboration with the Diagnostic Imaging Department, CC, has accomplished acquisition of minicomputer hardware and the development of software necessary to process data from three scintillation cameras in the Diagnostic Imaging Department.

The objective of this program is continuing development of computer based algorithms which have already found wide-ranging applications, including: fitting mathematical models; mapping the parameters of such models over time and in different regions of an organ; image processing; interpolation, expansion, and contraction of image arrays. Application to other noninvasive imaging systems such as ultrasonograms, and the incorporation of other physiologic signals with the imaging studies (e.g. ECG-gated heart studies) are also under investigation.

Progress during FY 78:

During FY 76-77 the extended nuclear utility (ENU) system was developed (ref. 1), which allowed the rapid modular construction of complex processing programs using newly developed program modules from a library of already developed algorithms. This system was used extensively in the development of radionuclide angiography, pulmonary scintigraphy, and radionuclide renography projects (ref. 2). During FY 78, the algorithms developed under ENU have been largely upgraded and re-implemented under the real time executive (RTE). RTE is a new vendor supported system which allows the nuclear medicine minicomputers to become multi-user, multi-task systems. RTE allows rapid development of modules which formerly could only be achieved under ENU.

Previous work in FY 76 showed a significant enhancement of radionuclide renography by the use of functional maps and since FY 77 functional maps have come into routine clinical use (ref. 3). Currently several dogs are being studied, before and after surgically induced segmental renovascular occlusions. These canine models will be used to document the sensitivity and specificity of functional maps in detecting and localizing renovascular disease.

Since FY 72, DI and LAS have collaborated upon development and refinement of algorithms to produce radionuclide angiograms and ventricular volume curves simultaneously while scintillation data is being collected from the patient (refs. 4-5). Usefulness of functional maps in this area also has been studied (ref. 6). In FY 76 a package of image processing routines (IMAGE) was developed on the PDP-10 System. This package is capable of several functions: e.g. edge detection, spatial derivatives, iterative deconvolution, noise detection and application of selective filters.

Progress during FY 78:

In FY 78 this image processing package was used to design an algorithm for automatic detection of the left ventricle in radionuclide angiocardiography (refs. 7-8). Currently the algorithm is being implemented on the nuclear medicine minicomputer system in order to facilitate the real time system. IMAGE was also used to design an automatic detection algorithm for kidneys. During FY 78 a Biomation hardware buffer was interfaced with a Picker ultrasound system and an HP minicomputer. A few abdominal ultrasonograms have been captured in digital form and displayed on the Evans and Sutherland device with color coding.

There has been continued development in pulmonary scintigraphy methods (see project on Computer-based Modeling of Pulmonary Gas Exchange and Respiratory Mechanics).

Significance:

Scintigraphy is a noninvasive tool which shows considerable detail concerning the dynamic function of an organ on a regional basis. Computer processing not only enhances scintillation images but allows quantification of the dynamic function. Real time implementation of algorithms on the minicomputers allows the clinical investigator to perform repeated studies on patients with exercise or therapeutic manipulation, thus better elucidating the nature of the patient's pathophysiology.

Ultrasonography is a diagnostic imaging tool with wide application. It offers an excellent opportunity to obtain serial studies of certain disease processes at frequent intervals non-invasively and without the risk of radiation exposure. Image enhancement and automatic pattern recognition should greatly improve its clinical utility.

Proposed Course:

The canine models will be extended to include obstructive nephropathy, toxic nephritis, and mass lesions (e.g. hematoma). When renal functional maps are validated by canine models, this noninvasive diagnostic method should greatly improve the evaluation of disease state and response to therapy in patients with lupus nephritis (NIAMDD), renal hypertension (NHLBI), and neoplasia affecting the kidneys and urinary tract (NCI).

NHLBI has solicited the collaboration of LAS and DI in studying Thallium 201 images of the myocardium as an adjunct to radionuclide angiography in detection of coronary disease (ref. 9).

Clinicians in the Diagnostic Imaging Department propose to study techniques for improving ultrasound imaging of abdominal structures. These include grey scale expansion and windowing, use of color, area measurement with possible extension to volume measurement, and reduction of spatial distortion.

Publications and Abstracts:

1. Line, B.R.: A command processing system for the analysis of scintigraphic data. In Brill, A.G. (Ed.): Proc. 5th International Conference on Information Processing in Medical Imaging. Nat. Tech. Info. Service, ORNL/BCTIC-2, June 1977, 5: pp. 456-467.

2. Dunham, R.G., Line, B.R., and Johnston, G.S.: A comprehensive software system for producing functional maps. In Howard, B.Y. (Ed.): Proceedings of Seventh Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine, Computer Assisted Data Processing. ERDA CONF-770101, 1977, 7: pp. 337-345.

3. Bradley-Moore, P.R., Klickna, J., Line, B.R., Jones, A.E., and Johnston, G.S.: Nuclear medicine reporting system--renal. In Howard, B.Y. (Ed.): Proceedings of Seventh Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine, Computer Assisted Data Processing. ERDA CONF-770101, 1977, 7: pp. 92-105.

4. Bacharach, S.L., Green, M.V., Borer, J.S., Line, B.R., Bradley-Moore, P.R., Ostrow, H.G., and Johnston, G.S.: Real-time collection, analysis and display of nuclear medicine data. Proc. 7th Symposium Comp. Prog. Tech. Nucl. Med., 1977 (in press).

5. Green, M.V., Brody, W.R., Douglas, M.A., Borer, J.S., Ostrow, H.G., Line, B.R., Bacharach, S.L., and Johnston, G.S.: Ejection fraction by count rate from gated images. Jour. Nucl. Med., 1978 (in press).

6. van Rijk, P.P., de Graaf, C.N., Jambroes, G., Bacharach, S.L., Green, M.V., Line, B.R., and Bailey, J.J.: Functional imaging in nuclear cardiac studies. Computers in Cardiology. IEEE Catalog No. 77CH2154-2C, IEEE Computer Society, Long Beach, Ca., 90803, 1978, pp. 9-17.

7. Douglas, M.A., and Green, M.V.: A System for Computer Generation of Left Ventricular Masks for use in Computerized ECG-Gated Radionuclide Angiocardiography. Nuclear Cardiology: Selected Computer Aspects. Society of Nuclear Medicine, New York, May 1978, pp. 119-128.

8. Green, M.V., Bacharach, S.L., Douglas, M.A., Borer, J.S., and Johnston, G.S.: Sources of Virtual Background in Multi-image Cardiac Studies. Nuclear Cardiology: Selected Computer Aspects. Society of Nuclear Medicine, New York, May 1978, pp. 97-106.

9. Douglas, M.A., Green, M.V., and Ostrow, H.G.: Computer Generation of left ventricular masks for use in computerized ECG-gated radionuclide angiocardiography. Computers in Cardiology, 1978 (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00006-08 LAS

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

General Mathematical and Computational Collaborative Efforts

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. Hill	Computer Systems Analyst	LAS DCRT
OTHER:	R. Shrager	Mathematician	LSMM DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A curve fitting methodology utilizing the Levenberg-Marquardt method for fitting non-linear models was extended to norms other than L (least squares). Heuristics are proposed and programs have been developed which offer these methods as practical tools. Manuscripts describing these methods have been submitted for publication.

A second project area involved a comparison of methods for organizing very large amounts of stored data which facilitate rapid storage and retrieval. Existing hashing methods were evaluated and new algorithms are proposed for very large data bases. A methodology for evaluation and comparison of schemes is described.

Curve Fitting

Background and Objectives:

This project is concerned with the development of two areas of computer applications and mathematics in the biosciences. The first area is concerned with Nonlinear Model Fitting and Parameter Estimation. The "standard" methods of least squares have been extensively developed for fitting nonlinear models to experimentally obtained data with estimation of unknown parameters in these models as a basic objective. For many applications, the least squares criteron is not appropriate and may introduce unnecessary computational difficulties. For example, fitting data taken over a wide range of values of the independent variables, and fitted without weights, tends to bias the results toward the data associated with larger values of the independent variables. The problems of ill-conditioning with systems having several parameters are also well known. Until recently, methods for fitting models with nonlinear parameters were not available with other than the least squares criteria. The first part of this project is concerned with such criteria.

Progress in FY 78:

In FY 78 the Levenberg-Marquardt Method for nonlinear curve-fitting in the L_1 Norm, ($L_1 = \text{Min} \sum_{1 \le i \le m} |y - y|_i$) and L_∞ norm, [$L_\infty = \text{Min Max } | \bar{y} - \hat{y} |]_i$ has been implemented in Fortran IV. Articles describing these methods and some applications have been submitted for publication.

Proposed Course:

The data fitting routines are available in DCRT computer library form. Applications will be made on an as required or requested basis. No further analytical development is anticipated in this area.

Large Data Bases

Background and Objectives:

A second project area involves a comparison of methods for organizing large amounts of stored data on direct access storage devices to facilitate fast retrieval of the desired information. This project was undertaken in order to classify the performance of the various retrieval methods and their associated data structures.

In a very large data base involving retrieval and updating, the major factor of immediate concern is the average number of accesses to the direct access storage device to complete a request. The average number of accesses to store and retrieve items on a direct access storage device was considered for hashing methods and other techniques.

Significance to Biomedical Research:

Such methodology has application to the design of storage and retrieval schemes for medical records, computer-aided diagnoses, medical linguistics, and other technical areas requiring search and retrieval in very large data or decision files.

Progress in FY 78:

The algorithms and performance measures described in FY 77 have been edited and published.

Proposed Course:

The algorithms developed from the described studies are available in DCRT computer libraries, and applications will be made as the need arises. No further analytical development is anticipated in this area.

Publications:

1. Shrager, R. and Hill, E.: Curve-fitting in the L_1 and L_∞ norms. SIAM Reviews, (Chronicle), April 1978.

2. Shrager, R. and Hill, E.: Some properties of the Levenberg method in the L_1 and L_∞ norms. Mathematics of Computations, 1978 (in press).

3. Hill, E.: A Comparative Study of Very Large Data Bases. Lecture Notes in Computer Science 59: January 1978.

4. Hill, E.: Analysis of an inverted data base structure, First International SIGIR Conference, May 1978.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00004-07 LAS

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Investigation of Hybrid Computing for the Construction of Simulation Models and for the Analysis of Physiologic Signals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.W. Pottala	Elec. Engineer	LAS	DCRT
OTHERS:	J.J. Bailey	Chief Medical Appl. Section	LAS	DCRT
	M.R. Horton	Computer Systems Analyst	LAS	DCRT
	R. Covacci	Visiting Scientist	LAS	DCRT
	S. Vallerga	Visiting Scientist	LNP	NINCDS
	A.R. Mitz	Elec. Engineer	LAS	DCRT
	R. Norman	Staff Fellow	LNP	NINCDS
	T.B. Stibolt	Senior Staff Fellow	LAS	DCRT
	M.A. Douglas	Computer Systems Analyst	LAS	DCRT

COOPERATING UNITS (if any)
Laboratory of Neurophysiology, NINCDS

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.1	2.0	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project was undertaken to develop physiologic simulation models using hybrid computing and also to use hybrid computing techniques to analyze physiologic signals such as electrocardiogram, electroencephalogram, ultrasonogram, and scintigram.

PHS-6040
(Rev. 10-76)

Background and Objectives:

In some simulation models, certain pieces or functions can be split off and implemented in hardware circuitry or a set of microprocessors. This has several advantages. First, parallel processing is allowed, which can shorten computing time and make interactive model testing feasible. Second, the hardware circuitry or microprocessors are usually quite inexpensive. And third, some models are so complicated and extensive, that their implementation on a large scale digital computer is not feasible; whereas with hybrid computing, such models may be achieved. An example was the model of the Purkinje network in the alligator cerebellum which required a system of 35 cells connected by nonlinear differential equations (completed in FY 76).

Since FY 72 the LAS Laboratory minicomputer system (MAC 16) has been developed and utilized for various projects including (1) the construction of physiologic simulation models and (2) the processing of physiologic signals. Since FY 72 the system has been interfaced with the Marquette tape drive (for routine ECG's from the Clinical Center); with the Honeywell 7600 analog tape transport; with a general purpose switch-filter network; with a real time spectral analyzer and ensemble averager; and with a neural control panel for simulation of neural networks (FY 75) and central nervous system subsystems (cerebellum, FY 76).

A general advantage of this system is that an investigator can automatically pre-process (edit, filter, and digitize) dynamic physiologic data so that optimal use of a large scale digital computer can be obtained. This was demonstrated in electromyograms from subjects on a muscle fatigue protocol studied by the National Institute of Occupational Safety and Health (FY 75). This facility was also used for electrocardiogram (ECG) and ventricular pressure data in monkeys (FY 76) and also ECG data from Glasgow Royal Infirmary (see ECG section).

Progress During FY 78:

The Laboratory of Neurophysiology, NINCDS, is studying the electrophysiology of the retina of the larvae tiger salmander. The Baylor-Hodgkin-Lamb model of a cone cell requires six compartments connected by six linear differential equations and three compartments involving sodium and potassium fluxes related by three nonlinear differential equations. This model has been implemented in hardware by LAS (ref. 1-2). It was also implemented in software on the PDP-10 so that the hardware model could be thoroughly checked out (ref. 3). The model parameters were adjusted to best fit the actual photoresponses (membrane potential) recorded intracellularly from cones in the retina of the larva tiger salamander. Stimuli consisted of flashes and steps of light. The responses of the model and the real cone cell were in good agreement for 10 millisecond flashes and 0.7 second steps of light whose intensities ranged over 2.5 log units with the intensity of the unattenuated light at 1.5 X 10**17 photons per second per square centimeter.

The LAS minicomputer system is being upgraded by the incorporation of a Micro-Arithmetic Processor (MAP). This hardware device can process large arrays very rapidly; for example, a Fast Fourier Transformation of 1024 data points can be produced in 20 milliseconds. The array processing capability will enable interactive design of filtering algorithms for many different physiologic signals and also the implementation of such filtering algorithms in real time.

Proposed Course:

Work will continue on the hybrid modeling system for retinal physiology consisting of hardware models of cone cells, rod cells, horizontal cells, and bipolar cells connected together in a network and driven by the LAS minicomputer system. This hybrid modeling system should permit a rapid test of possible synaptic configurations to determine the one which best fits observed photoresponses and eventually the designing of the proper electro-physiological experiments to verify it.

An operating system for the MAC-16 system will be developed which will provide the user with easy access to compilers and major programs, will handle I/O for all peripheral devices, and will automatically allocate system facilities and storage during execution of user programs.

The installation of the MAP will allow extensive studies into use of orthogonal transforms and other tools for filtering of physiologic signals and image enhancement algorithms for ultrasonographic and scintigraphic data.

Publications and Abstracts:

1. Pottala, E.W., Covacci, R., Colburn, T.R., and Vallerga, S.: Hardware model of a tiger salamander cone cell, Proceedings of the 30th ACEMB, Alliance for Engineering in Medicine and Biology, Bethesda, MD, 1977, pp. 369.

2. (ABSTRACT) Vallerga, S., Covacci, R., and Pottala, E.W.: Hardware simulation of cone cell photoresponse, Seventh Annual Meeting, Society of Neurosciences, Bethesda, MD, 1977, pp. 579.

3. (ABSTRACT) Covacci, R., Pottala, E.W., and Vallerga, S.: Cone responses: a computer-driven hardware model. 50th Anniversary Spring Meeting of the Association for Research in Vision and Ophthalmology, 1978, pp. 168.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00005-08 LAS

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Mathematical Modeling of Biological Processes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.E. Fletcher	Chief, Applied Mathematics Section	LAS	DCRT
OTHER:	M. Bieterman	Mathematician, AMS	LAS	DCRT
	A. Spector	Professor, Univ. of Iowa Med. School		
	B. Bunow	Biomathematician, AMS	LAS	DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project consists of three areas of investigation: (1) Mathematical Modeling of Substrate Transport in the Microcirculation, (2) Approximation Techniques and Numerical Methods for the Solution of Transport and Diffusion Processes in Biomedicine, and (3) Mathematical Models of Binding Equilibria. All areas have in common the development of conceptual models as mathematical formulations from basic physical, biochemical, or biomedical principles. Methods for solution via computer are studied; those which appear theoretically sound and efficient in practice are used to produce unknown parameters from experimental data, simulate laboratory experiments, and/or to validate experimentally determined ranges of variation in biomedical phenomena.

Objectives:

The objectives of this project are to develop mathematical models which can be used to simulate laboratory or clinical experiments and to explain, interpret and/or predict physiologic behavior and limits. Such models may lead to better understanding of basic biological processes and suggest new experimental approaches to problems of biomedical and biochemical importance. Because of manpower limitations, only a few such models can be considered in depth. These are detailed in the following paragraphs.

(1) Mathematical Modeling of Substrate Transport in the Microcirculation

Background:

The mathematical modeling of substrate supply to tissue from the microcirculation has been under study since FY 69. The tissue substrate of primary concern is tissue oxygen. Such studies are aimed at the prediction of threshold and critical limits of substrate supply necessary to sustain cell function under a variety of physiologic conditions. The responses of models to varying blood flow, hemoglobin characteristics, tissue metabloic rate and other physiologic parameters have been examined. The complex interaction of microcirculatory geometry, nonlinear oxygen dissociation properties, intracellular binding proteins, and substrate dependent metabolic rates requires such a detailed description to achieve physiologic validity. These models require the solution of coupled distributed parameter models which are of a nonlinear type.

Significance to Biomedical Research:

Such modeling is necessary to reconstruct local tissue microcirculatory dynamics since direct measurements are generally not possible and microcirculatory function must be inferred from boundary observations. Studies of this type are used to predict tissue oxygenation and reoxygenation in ischemia, hypoxia, anemia, coronary obstructions, sickle cell anemia and other conditions of substrate pathophysiology. Recent studies have considered the contribution of diffusion facilitation through oxygen binding to tissue myoglobin.

Progress in FY 78:

The contribution of binding proteins to substrate movement in tissue was considered in FY 78. A new model was developed which included the previously neglected effects of flow, capillary length and radius, and dissociation kinetics in capillary blood. The resulting mathematical model required nonclassical solution techniques; a methodology for the complete system of equations is currently being explored. Preliminary results with simplified versions indicate that diffusion facilitation can be quite important at low flow or high metabolic rate tissue conditions.

A review of existing modeling literature in this area in FY 78 resulted in a published review paper. This article is expected to attract and stimulate new modeling efforts on some of the more difficult and unresolved questions relating to tissue substrate supply.

Proposed Course:

Mathematical techniques for the solution of model equations will be explored for accuracy and applicability. New numerical techniques currently under development will be finalized and applied to the models describing the complex interactions of facilitation, metabolism, and blood-oxygen extractions. As the approximation technology is developed, efforts will be made to consider rhythmic or periodic conditions which relate more closely to cardiac and skeletal muscle function.

(2) Approximation Techniques and Numerical Methods for the Solution of Transport and Diffusion Processes in Biomedicine

Background:

The mathematical modeling of flow, transport, and chemical reaction in the microcirculation has generated mathematical models of a nonclassical type. Specific mathematical and numerical techniques to treat those equations were not available in the existing mathematical literature. The development of such techniques, and the continuing search for new efficient and economical techniques is the objective of this research area.

Significance to Biomedical Research:

The effective modeling of dynamic physiologic processes requires efficient methods for the numerical or approximate solution of systems of lumped or distributed parameter models. Such models are required to describe the complexity of dynamic interacting systems such as flow, diffusion, and chemical reaction basic to normal and pathophysiology. A key to parametric exploration and simulation by such models is clearly the ability to efficiently solve the model equations. The collection and characterization of such techniques also makes them available to the NIH biomedical community for its general use.

Progress in FY 78:

Numerical methods used to solve linear and nonlinear ordinary and partial differential equations describing physiologic flow and diffusion processes were investigated and implemented in computer programs. These programs are designed to be useable by those not expert in the relevant mathematical theory. The methods include finite difference techniques which are appropriate for biological transport problems and finite element methods, an approximation procedure studied

and used extensively in mathematics and structural engineering. This method has just recently been applied to models describing biological problems. Specifically, this method is incorporated in a novel iterative continuation scheme used to solve coupled nonlinear reaction-diffusion equations with flux boundary conditions. With respect to reliability, accuracy and cost, preliminary results compare favorably with published solutions of similar problems obtained by other techniques.

Proposed Course:

These programs can be used in more comprehensive studies than described in the above applications, and will form the basic tools for computing solutions to such models. Efficient and easy to use numerical methods will reduce the cost and decrease the time necessary to simulate a laboratory test or wet lab experiment. This effort will continue at a level of effort determined by section priorities and manpower.

(3) Mathematical Models of Binding Equilibria

Background:

Mathematical models of macromolecule-ligand binding equilibria, have been investigated since 1966. This continuing effort has revised many of the concepts related to the binding of ligands to macromolecules and has produced an interactive methodology for the fitting of models to data and other computer oriented tools for the analysis of data from laboratory experiments.

Significance to Biomedical Research:

The fitting of models to experimentally obtained data is a procedure used to determine unknown parameters in mathematical models. The proper choice of a model and the ability to determine the unknown parameters is a basic tool of biomedical research. Such procedures broaden biomedical knowledge and add to basic scientific knowledge only if the models represent the underlying biological process, and the unknown parameters can be readily and accurately determined. A thorough and continuing critique of such models and their validity for the interpretation of current laboratory and clinical experiments is therefore essential to the progress of science.

Progress in FY 78:

A generalized analysis of equilibrium models was completed and published in FY 78. Examples were constructed demonstrating the non-uniqueness of equilibrium models in predicting the microscopic binding process. Generalized computer programs to treat the alternative models were also developed. It is not anticipated that analytical work in this area will continue, although applications will continue, to be considered.

Proposed Course:

Applications of existing methodology to data analysis will continue to be made as they are requested by collaborating laboratories. Some new concepts in membrane-receptor studies are being considered and applications such as the analysis of cholesterol exchange in lipid bilayers are under study. The direction of this project will continue to be in the examination of the transport and exchange of lipids, fatty acids, and cholesterol in laboratory experiments.

Publications and Abstracts:

1. Spector, A.A., and Fletcher, J.E.: Nutitional Effects on Drug-Protein Binding. In Hathcock, J.N., and Coon, J. (Eds.): Nutrition and Drug Interrelations. New York, Academic Press, 1978 pp. 447-473.

2. Fletcher, J.E.: A generalized approach to equilibrium models. J. of Physical Chemistry 81: 2374, 1977.

3. Spector, A.A. and Fletcher, J.E.: Transport of Fatty Acid in the Circulation. In Dietschy, J.M., Dietschy, J.A., Ontko, J.A., and Gotto, A.M. (Eds.): The Physiology of Lipids and Lipoproteins in Health and in Disease. Bethesda, MD., American Physiological Society, 1978, pp. 229-249.

4. Fletcher, J.E. and Spector, A.A.: Alternative models for the analysis of drug-protein binding. Molecular Pharmacology 13: 387-399, 1977.

5. Spector, A.A. and Fletcher, J.E.: Fatty acid binding by serum albumin. In Peters, T., and Sjoholm, I. (Eds.): FEBS Federation of European Biochemical Societies, 11th Meeting Copenhagen 1977. New York, Pergamon Press, 1978, Vol. 50, Coll. B9, pp. 51-60.

6. Fletcher, J.E.: Mathematical modeling of the microcirculation. Math. Biosciences 38: 159-202, 1978.

7. Fletcher, J.E.: A singular perturbation solution for a model of facilitated diffusion in striated muscle tissues. SIAM National Meeting, May 25, 1978.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00035-02 LAS

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Mathematical Models and Simulation Programs in Physiology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. Hill Jr.	Computer Scientist	LAS	DCRT
OTHER:	J. Fletcher	Mathematician, Chief	LAS	DCRT
	E. Harris	Statistician, Chief	LAS	DCRT
	B. MacLees	Staff Physician	ICF	CC
	A. Robertson	Pathologist	CP	CC
	R. Elin	Pathologist, Chief	CP	CC

COOPERATING UNITS (if any)

None

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has as an objective the identification and classification of the various simulation programs used in physiology. These programs are being examined for utility in a clinical environment, accuracy of representation of normal and abnormal physiologic conditions, and the identification of areas of defective or missing physiologic relationships. Selected programs will be tested and evaluated in a teaching environment (Clin. Path. Dept., NIH) and an intensive care unit (Medical Intensive are facility, NIH).

Background and Objectives:

The objective of this project is to investigate the use of simulation programs in physiology as diagnostic and patient management aids to physicians and other clinical staff. A previous contractual effort, conducted in FY 77 by the George Washington University, has revealed that many such programs now in limited use are deficient in their physiologic description of interdependent metabolic pathways. One such deficiency, concerning acid-base balance, is now being considered in detail by this laboratory.

Significance to Biomedical Research:

Simulations offer the clinician the opportunity to try a proposed course of medical treatment on an ideal (computer) patient, without the attendant risk of injury to the actual patient.

Progress in FY 78:

The computer simulation of Electrolyte and Acid-Base Disorders is the first simulation program to be tried in a clinical setting at the NIH. This model was chosen because electrolyte and acid-base equilibrium data can be measured.

This program was developed by Dr. H. Bleich. Bleich's program is written in MIIS, a dialect of MUMPS. To make this program available at NIH on the IBM S/370 computers, it had to be translated to Standard MUMPS.

Considerable time was spent trying to convert Dr. Bleich's Acid-Base Program to Standard MUMPS. Two major software problems prevented the completion of this task. The first difficulty resulted from errors in the translator and the second problem arose from errors in the Standard MUMPS implemented on the S/370 computers.

After the translation efforts failed, a Fortran IV copy of the Bleich program was obtained from Dr. A. Forrey.

The I/O for this program was redesigned for the IBM S/370 computers at NIH. This program is now running on the NIH IBM S/370 computers and efforts are being made to evaluate the model's performance in a clinical setting.

Proposed Course:

Pending the outcome of feasibility studies, current trial applications, and manpower availability, future efforts will consider the development of physiologic simulators with accurate descriptions of interdependent pathways. Implementation of these programs in a variety of clinical settings will follow the developmental stage. Continuing efforts, requiring the cooperation of the Clinical Pathology Department (CC), will involve the testing of an acid-base

balance program with existing data on electrolyte, blood gas, and pH measurements from patients before and after specific therapeutic intervention.

Publications and reports:

None

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00007-10 LAS

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Statistical Research in Clinical Pathology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E.K. Harris	Chief, Lab. of Applied Studies	LAS	DCRT
OTHERS:	G. Shakarji	Supv. Systems Analyst	DMB	DCRT
	G.Z. Williams	Director, Institute for Health Research, San Francisco, Ca.		
	S.S. Brown	Clinical Chemistry Service Clinical Research Centre Harrow, England		
	E.A. Robertson	Clinical Pathology Department		CC

COOPERATING UNITS (if any)
None

LAB/BRANCH
Laboratory of Applied Studies

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In cooperation with Dr. G.Z. Williams and staff of the Health Research Institute (San Francisco), records of some 30 different biochemical and hematological tests performed annually over a 4-7 year period on several hundred healthy volunteers have been analyzed to test the adequacy and usefulness of 3 statistical forecasting models described in previous reports and publications. An initial report of this work is in preparation. The theory of Empirical Bayesian estimation has been explored to determine its usefulness as a way of improving estimates of individual mean values of biochemical constituents. Initially, applications to epidemiological studies have been investigated (Ref. 1). Work currently in progress tests the application of this theory to patient data from hospital laboratories. Another cooperative study examines the distribution of within-person variance in healthy volunteers and its effects on reference ranges and other medical diagnostic criteria. Finally, joint studies with cooperating pathologists have begun on the power of various statistical models and tests to detect short-term trends in biochemical quantities.

Objectives:

To investigate applications of statistical theory, particularly the use of variance components and the theory of discrete time series, to the interpretation of clinical laboratory measurements and the evaluation of analytic methods.

Background and Progress during FY 78:

The database gathered through the health monitoring program of the Health Research Institute (HRI), San Francisco, represents one of the largest extant collections of serial biochemistries on normal volunteers. Hence it offers an unusual opportunity to study the suitability of various recently published statistical models and analytic methods aimed at detecting step changes and trends in short series of biochemical data from healthy persons. During the past year, in cooperation with statistical and computing staff at HRI, data have been collated and analysis begun on over 30 biochemical and hematological analytes in several hundred individuals who have undergone at least 4 annual examinations, with several weekly retests around each time of examination. Preliminary results show that a nonstationary, random walk model of within-person variation is appropriate for a substantial proportion of individual series, particularly hematological variables. The practical effects of using a "critical forecasting range" based on both stationary and nonstationary models are being explored in this database. Initial studies are underway on the power of these models and related statistical tests to detect trends in short series of biochemistries in the presence of analytic and biological background variation.

Utilizing a smaller database of weekly measurements on 37 healthy male volunteers over a 5-month period, collected in a cooperative study with the Clinical Research Centre, Harrow, England, the second in a new series of reports on normal variation is being prepared. This analysis focuses on the heterogeneity of intrapersonal variation in each of 10 common analytes, and the effects of such heterogeneity on (a) width of reference ("normal") ranges and (b) the applicability of commonly accepted criteria concerning the amount of change between succesive observations which should trigger investigative medical activity.

A common problem in epidemiological studies and in the interpretation of hospital laboratory data is the inaccuracy of a single observation as an estimate of an individual's underlying true value (e.g., blood pressure, alkaline phosphatase, etc, etc.). During this past year, an intensive study, both theoretical and applied to real data, was undertaken of Empirical Bayesian estimation procedures to improve the accuracy of single measurements. These methods involve replacing the individual observation by a weighted average of the observation and the mean of a reference distribution. The expected gain in accuracy depends partly on whether the single measurement is typical or extreme, partly on the ratio of average within-person to between-person variation. An initial publication of results useful for epidemiological studies will appear in late 1978 or early 1979 (Ref. 1). The process of collecting a

suitable database to test the usefulness of Empirical Bayes estimates in assessing clinical laboratory reports is just beginning in cooperation with the Clinical Pathology Department, CC, NIH.

It was previously reported that statistical criteria to determine suitable goals for the accuracy and precision of clinical laboratory test methods had been developed in response to a request from the College of American Pathologists (CAP). These criteria were based on stochastic models of within-person variation which, together with earlier estimates of physiological and analytic variance, were applied to several realistic contexts of use of laboratory tests. The invited paper part of a conference on the subject of analytic goals sponsored by the CAP was published during FY 78 (Ref. 2). In April, 1978, in concert with representatives of the CAP, these statistical principles were presented to European pathologists at a conference in London under the aegis of the World Association of Societies of Pathology. Recommendations of this meeting are expected to be transmitted to the World Health Organization for distribution to member nations who may wish to apply them in accordance with specific national needs.

Significance to Biomedical Research:

The definition and estimation of analytic and biological variance components provides an essential basis for the objective interpretation of clinical laboratory tests in patients and healthy persons alike. The development, testing and eventual routine use of stochastic models to describe and forecast sequential results of laboratory tests in individual cases has already proven useful when applied to periodic monitoring of healthy individuals as part of a general program of preventive medicine. These methods of data analysis require the use of standard computer program packages as well as construction and implementation of special algorithms for computer-based laboratory reporting systems. A spin-off from these research efforts has been the development of versatile computer systems for storing, updating and retrieving serial information on multiple laboratory results for individual patients. These systems are currently being employed in the Hypertension-Endocrine Branch (NHLBI) and the Arthritis and Rheumatism Branch (NIAMDD). These developmental and associated consulting activities have expanded the services which DCRT offers the NIH clinical community.

Future Course:

Collaborative analysis of data collected by the Health Research Institute to determine the relative usefulness of stationary vs. non-stationary models for detecting step changes in serial biochemistries of normal subjects will probably be concluded during FY 79, as will the analysis of variance heterogeneity based on the more intensive study undertaken at the Clinical Research Centre near London. Studies with the Clinical Pathology Department at NIH on application of Empirical Bayesian methods to laboratory data are expected to deepen during the coming year, while investigations into the power of statistical

models to detect trends in short series of biochemical measurements will expand further, utilizing data from various clinical laboratories.

Publications:

1. Harris, E.K. and Shakarji, G.: Use of the population distribution to improve estimation of individual means in epidemiological studies. J. Chronic Diseases, 1978 (in press).

2. Harris, E.K.: Statistical principles underlying analytic goal-setting in clinical chemistry. Proceedings of the College of American Pathologists Second Annual Aspen Conference (1976) on Analytical Goals in Clinical Chemistry, pp. 115-135, 1977; to be reprinted as a supplement to the Amer. J. of Clinical Pathology, Summer, 1979.

October 1, 1977 through September 30, 1978

NATIONAL INSTITUTES OF HEALTH
DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Summary of Branch Activities

1. DCRT

2. PHYSICAL SCIENCES LABORATORY

3. George H. Weiss
Chief

I. SUMMARY

Function

The Physical Sciences Laboratory has three principal functions:

- to carry out research in the physical sciences in order to understand biological phenomena in terms of physics and chemistry
- to develop the theory and practical instrumentation for biomedical experiments, and in particular to relate these to the capabilities of modern computer technology
- to provide consulting services to other scientists at NIH in physics, theoretical chemistry, and several fields in applied mathematics.

The staff of the Physical Sciences Laboratory consists of six professionals who work in the areas of general biophysics, nuclear magnetic resonance, applications of light scattering techniques in biomedical experiments, the physical chemistry of polyelectrolytes and problems in applied mathematics.

Scope of Work

The Physical Sciences Laboratory has a combined program of research projects internal to the laboratory and collaborative projects with scientists at NIH and at other institutions. These collaborative projects are done jointly with approximately ten other investigators including two major projects with data being generated by off-campus scientists.

Highlights of the Year's Activities

During the past year the members of the Physical Sciences Laboratory have made significant progress in projects started in past years, as well as initiating a few new ones.

Dr. Ferretti continued his studies of the application of NMR techniques to determining conformational properties of small proteins. A particularly interesting investigation recently begun is the determination of the

metal ion binding sites of bleomycin, an important agent in cancer chemotherapy. Considerable progress has been made in assigning the resonance of the C^{13} NMR spectra of bleomycin.

Drs. Parsegian and Tinker conducted an extensive survey of electrostatic interactions in proteins, using the computer programs developed by Richard Feldmann of DCRT. They discovered several features of such interactions that help to maintain contact within proteins by an intricate matching of positive and negative charges.

Drs. Nossal and Brenner continued work on the application of laser spectroscopy to the measurement of elastic properties of biological gels. Experiments are in progress to apply Doppler laser techniques to measure tissue blood flow.

Drs. Darvey and Weiss developed a theory allowing one to specify optimal designs and analyses of biochemical kinetic measurements. They have examined the effects of different weighting schemes for least-squares analysis of the data, as well as the effects of choosing different substrate concentrations on the accuracy of estimates of the kinetic parameters. Dr. Weiss has developed a general theory of interpolation error in computerized tomography with parallel ray machines. The results enable one to choose the number of views required to achieve given resolution.

Dr. Nossal has been appointed to the Board of Editors of the Biophysical Journal and Dr. Weiss has been appointed to that of Separation Science and Technology. Dr. Parsegian has been presented with the NIH Director's Award.

Theory and Application of Nuclear Magnetic Resonance Spectroscopy

A continuing subject of investigation is the optimal design of NMR experiments to insure specified accuracy in the determination of relaxation times in the minimum time. We have found that time savings of the order of 30% can be achieved by proper design, over the standard inversion-recovery method. Different approximation techniques are being applied to the Bloch equation to extend its use to situations of experimental use. In particular, perturbation theory has been used to demonstrate that correlation spectroscopy is practical even when the spin system is driven into a nonlinear response region.

Consulting Services

A considerable amount of time has been spent in developing techniques to correct and query a large data base on head injured veterans of Vietnam. An important conclusion allowed by our work to date is that the use of anticonvulsant drugs has not led to a decrease in the indicence of post traumatic epilepsy. A further problem in which progress has been made is that of interpolation error in computerized tomography. We have developed an error analysis applicable to asymmetric objects that allows one to relate the errors to the number of views available and to the interpolation method that is used.

II. PSL PROJECTS AND ACTIVITIES FY 78

Theory of Biochemical Separation Techniques. George H. Weiss, PSL, in collaboration with Dr. D. A. Yphantis, University of Connecticut. This project develops mathematical theory for the planning and interpretation of experiments with such techniques as chromatography, electrophoresis, and ultracentrifugation.

The Role of Electrostatic Forces in the Organization and Properties of Macromolecular Systems. Stephen L. Brenner, PSL, V. A. Parsegian, PSL. This project studies the role of electrostatic forces in determining the mutual arrangement and interaction of macromolecules in aqueous salt solutions. (This project is inactive)

Theory and Application of Nuclear Magnetic Resonance Spectroscopy. James A. Ferretti, PSL, George H. Weiss, PSL. This project includes the development of new methodology in nuclear magnetic resonance and the application of NMR to elucidate chemical properties of molecules of biological interest.

Correlation Function Spectroscopy/Laser Light Scattering. Ralph J. Nossal, PSL, Stephen Brenner, PSL. The laser inelastic light scattering spectrometer is being used to measure elastic parameters of gels as well as parameters of cell motility. Several collaborative experiments are being planned using optical techniques developed by this project.

Cell Motility and Chemotaxis. Ralph J. Nossal, PSL, Stephen L. Brenner, PSL, and George H. Weiss, PSL. This project develops methodology for the interpretation of experiments related to cell locomotion and chemotaxis.

Theory and Measurement of Intermolecular Forces. V. A. Parsegian, PSL, George H. Weiss, PSL, James E. Kiefer, PSL. The object of these studies is to develop the theory of electrodynamic forces in biological media, and to develop experimental methods for measuring these forces.

Studies in Mathematics and Statistics . George H. Weiss, PSL, James E. Kiefer, PSL. Several disparate studies are included in the project. The present set of studies include the optimization of enzyme kinetic experiments, and an analysis of the dimensions of contrained polymer chains.

Consulting Services. George H. Weiss, PSL, Ralph J. Nossal, PSL, and James E. Kiefer, PSL. Members of the PSL give consulting assistance to other scientists at NIH and elsewhere, in the areas of the physical sciences and applied mathematics.

III. PUBLICATIONS

Blumenfeld, D. E., Weiss, G. H.: Sampling errors in the measurement of traffic noise. J. Sound and Vib. 53, 111-116 (1977).

Blumenfeld, D. E., Weiss, G. H.: Curve fitting the probability distribution of acoustic noise from freely flowing traffic. Transp. Res. 12, 111-114 (1978).

Blumenfeld, D. E., Weiss, G. H.: Can nonlocal gap acceptance functions be distinguished from local ones? Transp. Res. (to appear).

Brenner, S. L., Nossal, R. J.: Correlation functions for light scattering from soft gels. Macromol. 11, 207-212 (1978).

Brenner, S. L., Gelman, R. A., Nossal, R. J.: Laser light scattering from soft gels. Macromol. 11, 202-207 (1978).

Brenner, S. L., Nossal, R. J., Weiss, G. H.: Number fluctuation analysis of random locomotion. J. Stat. Phys. 18, 1-18 (1978).

Brenner, S. L., Parsegian, V. A., Gingell, D.: The effects of image forces on double-layer interactions. J. Phys. Chem. (to appear).

Brooks, R. A., Weiss, G. H., Talbert, A.: A new approach to interpolation in computed tomography. J. Computerized Tomog. (to appear).

Chew, D., Weiss, G. H., Brooks, R. A., Di Chiro, G .: Effect of noise on the detectability of test objects. Am. J. Roentgen. (to appear).

Correia, J. J., Weiss, G. H., Yphantis, D. A.: An extrapolation method for reducing equilibration times in sedimentation equilibrium experiments. Biophys. J. 20, 153-168 (1977).

Cowley, S., Fuller, N., Rand, R. P., Parsegian, V . A.: Measurement of repulsion between charged phospholipid bilayers. Biochem. (to appear).

Dishon, M., Weiss, G . H.: When do transient double peaks occur in pH gradient electrophoresis? Analyt. Biochem. 81, 1-9 (1977).

Dishon, M., Weiss, G. H.: Numerical inversion of Mellin and two-sided Laplace transforms. J. Comp. Phys. (to appear).

Gail, M. H., Weiss, G. H., Mantel, M., O'Brien, S. J.: A solution to the generalized birthday problem with application to allozyme screening. J. Appl. Prob. (to appear).

Gingell, D., Parsegian, V. A., Todd, I.: Experimental evidence for long-range attraction between a red cell and a hydrocarbon surface. Nature 268, 767-768 (1977).

Kiefer, J. E., Parsegian, V. A., Weiss, G. H.: An easily calculated approximation for the many-body van der Waals attraction between sphere and wall. J.Coll. Interf.Sci. 63, 161-162 (1978).

Kiefer, J. E., Parsegian, V. A., Weiss, G. H.: Some convenient bounds and approximations for the many body van der Walls attraction between spheres. J. Coll. Interf. Sci. (to appear).

Lis, L. J., Rand, R. P., Parsegian, V. A.: Measurement of electrostatic forces between lecithin bilayers charged by divalent cations. Biophys. J. 21, 213a (1978).

McAlister, M., Fuller, N., Rand, R. P., Parsegian, V. A.: Measurement of surface pressure in and repulsion between approaching phospholipid membranes. Biophys. J. 21, 213a (1978).

McNeil, D. R., Weiss, G. H.: A large population approach to the estimation of parameters in Markov population models. Biometrika 64, 553-558 (1977).

Nossal, R. J.: Quasielastic laser light scattering by flexible polymer networks. J. Appl. Phys. (to appear).

Nossal, R. J.: Factors affecting the reliability of capillar MIF (Migration Inhibition Factor) assays, in Theoretical Immunology, Marcel Decker, 1978, 121-142.

Oppenheim, I. O., Shuler, K. E., Weiss, G. H.: Stochastic theory of nonlinear rate processes with multiple stationary states. Physica 88A, 191-214 (1977).

Parsegian, V. A., Weiss, G. H., Schrader, M. E.: Macroscopic continuum model of influence of hydrocarbon contaminant on forces causing wetting of gold by water. J. Coll. Interf. Sci. 61, 356-361 (1977).

Parsegian, V. A.: Considerations in determining the mode of influence of calcium on vesicle membrane interaction. Soc. for Neurosci. Symp. II. 161-171 (177).

Rubin, R . J., Weiss, G. H.: Boundaries of constrained random flight polymer chains. Macromol. (to appear).

Rubin, R. J., Weiss, G. H.: Span of a random flight model of a star-branched polymer chain. Macromol. 10, 332-334 (1977).

Simon, R., Hoel, D. G., Weiss, G. H.: The use of covariate information in dichotomous response experiments. Comm. in Stat.. A6, 777-788 (1978).

Tinker, D. O., Parsegian, V. A.: Interactions between subunits of protein oligomers. Biophys. J. 145a, 142 (1978).

Weiss, G. H.: Comments of a model of polymer growth. J. Coll. Interf. Sci. 61, 199200 (1977).

Weiss, G. H., Brooks, R. A.: Integration errors in image reconstruction of circularly symmetric objects. Theory and Application of Statistical Mechanics, Plenum Press, 1977, 669-684.

Weiss, G. H.: Transport equations with quadratic nonlinearities. Sep. Sci. and Technol. (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00017-06 PSL

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Cell Motility and Chemotaxis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. J. Nossal, Research Physicist, PSL, DCRT
Other: G. H. Weiss, Chief, PSL,DCRT
S. L. Brenner, Staff Fellow, PSL,DCRT

COOPERATING UNITS (if any)

L. Lipkin, M.D., Image Processing Unit, DCBD, NCI

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.5	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project has been undertaken to study various aspects of cell locomotion and chemotaxis. Analytical expressions to quantitate capillary migration (MIF) assays have been derived. New procedures for measuring macroscopic coefficients of cell migration are being developed, including computer assisted tracking techniques. Studies of the manner in which lymphokines affect the migration of individual leukocytes are in progress.

Cell Motility and Chemotaxis

This study concerns phenomena relating to cell locomotion and chemotaxis. Recent emphasis has been on examining certain immunologic aspects of leukocyte migration.

Recently, as part of this project, a general mathematical theory for interpreting results of capillary migration assays for cellular immune sensitivity (MIF tests) was derived. However, various basic parameters of leukocyte movement which are necessary for quantitating the assay are not well-known. Consequently, collaborative experiments now are being performed with Dr. Lewis Lipkin (DCBD/NCI) which involve studying the response of neutrophils to various chemical factors ("lymphokines") produced by stimulated lymphocytes. Specialized measurement techniques have been devised, an example of which is a scheme where occupation number fluctuations are analyzed to determine mobility coefficients of migrating cells. Also, algorithms and computer programs have been developed in order to adapt an automated microscope system for cell tracking experiments. In addition, this instrument will be used to examine the behavior of neutrophils when responding to chemoattractants

Publications:

Nossal, R.: Factors affecting the reliability of capillar MIF (Migration Inhibition Factor) assays. Chapter 5 in Theoretical Immunology, ed. G. I. Bell, A. S. Perelson and G . H. Pimbley, Marcel Dekker, N.Y., pp. 121-142 (1978).

Brenner, S. L., Nossal, R. and Weiss, G. H.: Number fluctuation analysis of random locomotion. Statistics of a Smoluchowski process. J. Stat. Phys. 18, 1-18 (1978).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00022-11 PSL

PERIOD COVERED

October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Consulting Services

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. H. Weiss, Chief, Physical Sciences Laboratory,PSL,DCRT

COOPERATING UNITS (if any)

W. F. Caveness, M.D., Chief, LEN, NINCDS
R. A. Brooks, Ph.D., SN, NINCDS
M. H. Gail, M.D., Ph.D., Biometry, NCI

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Members of the Physical Sciences Laboratory provide consulting services to the scientists and physicians at NIH in the areas of applied mathematics, statistics, and the physical sciences. A continuing project is the construction and querying of a large data base on head injured veterans of Vietnam. We have also developed an error theory for interpolation in computerized tomography In a third project we have developed an accurate approximate solution to the generalized birthday problem, a classical problem in probability, with application to a genetic assay .

Consulting Services

A large effort has been put into the correction and querying of a large data base on head injured Vietnam veterans. Most of the effort has been in the correction of coding errors and errors that have been made in misinterpretation of battlefield and hospital records. So far approximately 13,000 records on 1,030 veterans are included in the data base. Several studies are either being planned or are presently in progress. Among these are the effects of anticonvulsant drugs on the supression of post traumatic epilepsy, and the utility of different operations on veterans with injuries to both lobes. A preliminary conclusion of the analysis is that treatment with anticonvulsant drugs does not lessen the incidence of past traumatic epilepsy. This conclusion follows by a comparison of data from the Vietnam war with data from the two World wars and the Korean war. This work was done as a collaborative with Dr. W. F. Caveness, NINCDS, and several other neurosurgeons outside of NIH.

We have continued our study of interpolation errors in computerized axial tomography with Dr. Rodney Brooks of NINCDS. Specifically we have derived a formula for the interpolation error due to an offset delta function image. This will enable us to study the interpolation error for asymmetric images. Another study on computerized axial tomography relates to the effects of noise on the identification of output images. Together with E. Chew of the University of Maryland and R. A. Brooks we designed and analyzed an experiment to test whether smoothing helps in the detection of different images and whether there is any difference in detectability when images are presented on a console or as polaroid pictures. We found, using 50 untrained observers and 8 radiologists that smoothing improves detectability in some, but not all, instances, and that there are no significant differences in presentation by console or by photograph.

Together with Dr. Mitchell Gail of NCI we have derived an accurate approximate solution to the generalized birthday problem. This problem arises in the context of a genetic assay. The solution to the problem involves a novel form of perturbation theory and may be applicable to many other combinatorial problems. The theory was tested on assay data furnished by S. J. O'Brien, NCI, on the contamination of cell cultures. The theory was found to be accurate over the entire range of probabilities.

Keyword Descriptors: Head injuries, post traumatic, epilepsy, anticonvulsant drugs, computerized axial tomography, interpolation errors, smoothing, birthday problem.

Publications:

Weiss, G. H. and Brooks, R. A.: Integration errors in image reconstructi of circularly symmetric objects in Theory and Application of Statistical Mechanics, Plenum Press, 1977, 669-684.

Chew, E., Weiss, G. H., Brooks, R. A., Di Chiro, G.: Effect of noise on the detectability of test objects. Am. J. Roentgenology (to appear)

Gail, M. H., Weiss, G. H., Mantel, N., O'Brien, S. J.: A solution to the generalized birthday problem with application to allozyme screening. J. Appl. Prob. (to appear).

Brooks, R. A., Weiss, G. H., Talbert, A. J.: A new approach to interpolation in computed tomography. J. Computed. Tomog. (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00021-07 PSL

PERIOD COVERED

October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Correlation Function Spectroscopy/Laser Light Scattering

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. J. Nossal, Ph.D., Research Physicist, PSL, DCRT
Other: S. L. Brenner, Ph.D., Staff Fellow, PSL,DCRT

COOPERATING UNITS (if any)

H. Saroff, Ph.D., Laboratory of Biophysical Chemistry, NIAMDD
J. Gladner, Ph.D., Laboratory of Biophysical Chemistry, NIAMDD
R. Bonner, Biomedical Engineering & Instrumentation Branch, DRS

LAB/BRANCH R. Gelman, Ph.D., Laboratory of Biochemistry, NIDR
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Div. of Computer Research & Technology, NIH, Bethesda, Md.

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.9	0.7	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Experimental and theoretical studies have been performed to develop laser inelastic light scattering methods for studying biological gels. The technique is being used to examine the strength of fibrin clots. Other studies are being performed in order to understand how laser Doppler techniques can be used to measure capillary blood flow in tissues.

FHS-6040
(Rev. 10-76)

Correlation Function Spectroscopy/Laser Light Scattering

The primary objective of this project is development of laser inelastic light scattering techniques for performing rapid and precise measurements on biological systems and materials. In principle, any process giving rise to refractive index fluctuations can be monitored. The instrument which we have constructed has been used to measure diffusion coefficients of macromolecules, swimming speed distributions of motile microorganisms, elastic moduli of gels and blood flow in capillaries.

During the past year we perfected a scheme for measuring elastic coefficients of dilute polymer networks and soft biological gels. Several collaborative studies utilizing this new technique are in progress; one, for example, involves relating the mechanical strength of fibrin clots to the nature and extent of interchain cross-linking (with H. Gladner, NIAMDD). Techniques for studying stiff gels also have been devised, and experiments with polyacrylamide gel models have been performed (with R. Gelman, NIDR). Necessary mathematical theory has been developed.

Also, experiments have been undertaken in regard to laser Doppler measurements of tissue blood flow. Dr. R. Bonner (BEIB) is developing a laser Doppler flowmeter for clinical use, and our spectrometer is being used to examine related questions concerning light scattering from surface microvasculature. Synthetic flow models have been devised to explore relationships between measured spectra and such variables as blood density, flow rate and back-scatter illumination from surrounding tissue.

Keyword Descriptors:

Laser light scattering, macromolecules, diffusion coefficients, correlation functions, gels, blood flow.

Publications:

Brenner, S. L. and Nossal, R.: Correlation Functions for light scattering from soft gels. Macromolecules 11, 207-212 (1978).

Brenner, S. L., Gelman, R. A., and Nossal, R. J.: Laser light scattering from soft gels. Macromolecules 11, 202-207 (1978).

Nossal, R.: Quasielastic laser light scattering by flexible polymer networks. J. Appl. Phys. (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00024-03 PSL

PERIOD COVERED

October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Studies in Mathematics and Statistics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: George H. Weiss, Chief, Phys. Sci. Lab, PSL, DCRT

Other: D. G. Hoel, Chief, Biometry Branch, EBB, NIEHS
D. E. Blumenfeld, Lecturer, University College, London
R. J. Rubin, Senior Scientist, NBS
I. G. Darvey, Visiting Scientist, PSL, DCRT
D. O. Tinker, Visiting Scientist, PSL, DCRT
J. E. Kiefer, Research Mathematician, PSL, DCRT

COOPERATING UNITS (if any)

None

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Division of Computer Research & Technology, NIH, Bethesda, MD. 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project includes several unrelated studies in applied mathematics Most of the time spent on this project was in the are of optimization of enzyme kinetics experiments. Methodology was developed for enzymes that follow Michaelis-Menten kinetics. Further work was done on the theory of the dimensions of constrained polymer chains.

PHS-6040
(Rev. 10-76)

Studies in Mathematics and Statistics

We have examined several aspects of the problem of optimizing kinetic experiments for enzymes that follow Michaelis-Menten kinetics. The first is a specification of the types of error that can occur in kinetic experiments, i.e., instrumental and pipetting errors. These have different effects on the behavior of observed variances of measured initial velocities as a function of the variable parameters. In particular, we have been able to explain some experimental measurements in the biochemical literature on the basis of the distinction between absolute and relative errors suggested by an analysis of error sources. A second problem relates to the specification of optimal sets of substrate concentration for single stage design of Michaelis-Menten experiments. A third problem in this area involves the comparison of different forms of weighting in least squares analysis of Michaelis-Menten experiments. This project involved simulation of the experiments and data analysis on both the nonlinear and linearized form of the equations. Surprisingly, a properly weighted form of the linearized equation led to the most accurate determinati of parameters. Our results suggested the use of hybrid weighting for improved accuracy. This does not seem to have been discussed before in the statistical literature. A subject for further investigation is that of two stage optimization in which data collected in the first stage is used for optimization in the second stage of an experiment.

We have, in collaboration with Dr. R. J. Rubin, analyzed the maximum extension of polymer chains that are constrained in various ways by using random walk models.

Keyword Descriptors: experimental design, Michaelis-Menten reactions least squares analysis, simulation, polymer chains.

Publications:

Oppenheim, I. O., Shuler, K. E., Weiss, G. H.: Stochastic theory of nonlinear rate processes with multiple stationary states. Physica 88A, 191-214 (1977).

Weiss, G. H.: Comments on a model of polymer growth. J. Coll. Interf. Sci., 61, 199-200 (1977)

Simon, R., Hoel, D. G., Weiss, G. H.: The use of covariate information in the sequential analysis of dichotomous response experiments. Comm. in Stat. A6, 777-788 (1977).

Blumenfeld, D. E., Weiss, G.H.: Sampling errors in the measurement of traffic noise. J. Sound and Vib. 53, 111-116 (1977).

McNeil, D. R ., Weiss, G. H.: A large population approach to estimation of parameters in Markov population models. Biometrika 64, 553-558 (1977).

Blumenfeld, D. E., Weiss, G. H.: Curve fitting the probability distribution of acoustic noise from freely flowing traffic. Transp. Res. 12, 111-114 (1978).

Dishon, M., Weiss, G. H.: Numerical inversion of Mellin and two-sided Laplace transforms. J. Comp. Phys. (to appear).

Rubin, R. J., Weiss, G. H.: Span of random flight model of a star-branched polymer chain. Macromol. 10, 332-334 (1977).

Blumenfeld, D. E., Weiss, G. H.: Can nonlocal gap acceptance functions be distinguised from local ones? Transp. Res. (to appear).

Rubin, R. J., Weiss, G. H.: Boundaries of constrained random flight polymer chains. Macromol (to appear).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00025-03 PSL

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Theory and Application of Nuclear Magnetic Resonance Spectroscopy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: James A. Ferretti Ph.D., Research Chemist, PSL,DCRT

Other: E. D. Becker, Chief, Laboratory of Chemical Physics, LCP,NIAMDD

G. R. Marshall Professor of Physiology, Dept. of Physiology, and Biophysics, Washington University School of Medicine, St. Louis, Mo.

G. H. Weiss, Chief, Physical Sciences Laboratory, PSL,DCRT

COOPERATING UNITS (if any)

Laboratory of Chemical Physics, NIAMDD

LAB/BRANCH

Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION

Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to develop new methods in nuclear magnetic resonance spectroscopy and also to apply NMR to the study of small proteins. In particular, development of the correlation method of obtaining NMR spectra is of special interest. An experimental and theoretical study of interference effects in correlation spectroscopy has been undertaken. Saturation effects in correlation NMR are currently being studied. Investigations of the solution conformation of derivatives of Angiotensin, Bradykinin and Bleomycin are in progress. In these systems we have demonstrated the importance of the contribution of internal motion to the relaxation behavior.

PHS-6040
(Rev. 10-76)

We are continuing to study spin-lattice relaxation times, T_1, spin-spin relaxation times, T_2 and nuclear Overhauser enhancement (NOE) factors in small peptide systems. These systems include Angiotensin II, Bradykinin, Tetragastrin, and various derivatives. The magnetic field dependence of T_1, T_2 and the NOE has been carried out at 25 MHz, 45 MHz, and 67.9 MHz, for the aliphatic carbon atoms of these various peptide systems. From these data we have been able to evaluate the effective correlation times for both overall and internal rotation in these molecules. The studies have allowed us to specify the nature of the molecular association in solution as well as to study the effects of constraints at the receptor-bound conformation of these hormones. Another important conclusion demonstrated by these studies is that the neglect of internal flexibility of these molecules leads to erroneous conclusions concerning the magnitudes of the overall correlation times. Measurements at a minimum of two magnetic field strengths are necessary to evaluate these molecular parameters.

We have initiated studies on Bleomycin (m.w. $\sim$ 1500). It is a glycopeptide antibiotic of low toxicity and is effective against a variety of human neoplasms. Its complexes with radioactive metals are useful as tumor scanning agents for diagnostic purposes. While the Cu(II), Zn(II), and Co(II) derivatives of Bleomycin are inactive, the Fe(II) complex exhibits enhanced DNA degrading activity. Initially we studied the carbon-13 NMR spectra of Bleomycin and completely assigned all the 55 resonances. We have also carried out T_1 and NOE studies at 45 MHz and 67.9 MHz as the basis for carrying out metal ion binding studies. Preliminary results on Cu(II) and Mn(II) have permitted us to locate tentatively the metal ion binding site in Bleomycin.

Non-linear effect including saturation in NMR correlation spectroscopy of uncoupled spin systems has been investigated. The basis of this study has been to carry out a perturbation expansion of the Bloch equation in order to obtain the first correction term to the response of the spin system. We find that for slow sweep rates, the rules of correlation spectroscopy hold only for very low power levels. In the case of fast passage the rules hold for power levels which correspond to effective flip angles of at least 60°. These results demonstrate the practicality of correlation spectroscopy even when the spin system is driven into a non-linear response region.

We have continued to analyze various aspects of NMR spin-lattice relaxation time T_1, studies determined by the inversion-recovery, fast inversion-recovery and saturation recovery methods. We have found under which conditions fast inversion-recovery or saturation recovery should be the selected technique. We find that under optimum conditions, typical time savings of about 30 percent may be realized relative to the standard inversion-recovery method.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00026-03 PSL

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Theory and Measurement of Intermolecular Forces

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: V. A. Parsegian, PSL,DCRT
G. H. Weiss, PSL,DCRT
D. O. Tinker, University of Toronto
J. E. Kiefer, PSL, DCRT

Others: R. P. Rand, Brock University
L. Lis, Brock University
S. Cowley, Brock University
M. McAlister, Brock University
N. Fuller, Brock University
D. Gingell, Middlesex Medical School

COOPERATING UNITS (if any)
None

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Division of Computer Research & Technology, NIH, Bethesda, MD

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2	2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project aims to understand the role of long range forces in biological phenomena. A major topic has been the measurement of forces between phospholipid bilayer membranes immersed in water. We are also measuring intermolecular forces between lipids in the same membrane. A new technique has been devised for detecting the reaction of charged particles with membrane surfaces.

Using the DCRT electronic display we have found two classes of forces between protein molecules forming dimers and tetramers (such as hemoglobin). These are intricate fitting of electrostatic charges and contact between hydrocarbon surfaces which are repelled by water.

Theory and Measurement of Intermolecular Forces

We continue to progress in developing methods for computing and detecting intermolecular forces. This has been accomplished in model cell membranes immersed in water, cells adhering to surfaces, protein particles forming functioning dimers and oligomers and in the reaction of charged particles with membrane surfaces.

With Professor Peter Rand of Brock University we have successfully made measurements of forces between phospholipid bilayer membranes. This includes several estimates of the van der Waals force between bodies in water. The results published so far are the beginning of a series of systematic studies on the physical properties of cell membrane lipids. We hope to extend these then to direct observations of forces between natural cell membranes. So far we have worked successfully with several model preparations. We have measured the important electrostatic repulsion between charged membranes. We have been able to measure also forces between molecules within the same membrane. This finding has opened up new means to determine the mechanical properties of artificial and natural membranes.

In one particular instance we have observed the adsorption of charged particles (ions) to membrane surfaces by measuring the effect of that adsorption on electrical forces between membranes. The force measurement then becomes a measure of the reactivity of ion with surface as it depends on electrical potential of the reacting surfaces, distance between membranes, and the ionic conditions of the bathing medium.

We have analyzed the contact of chemical delivering vesicles with nerve membranes to distinguish the role of vesicle membrane nerve membrane forces. It seems that the enormous forces required to remove water from membrane surfaces act as a serious barrier to contact and to the fusion of vescicle and membrane necessary for delivery of chemicals across the nerve wall. From our new knowledge of these forces it appears that chemical modification of membrane must occur to allow chemical release from nerve.

With Dr. David Gingell of London, England, we have been studying the interactions of red cells with each other and with artificial materials. Guided by the theory of forces as developed in this laboratory, we have devised experiments demonstrating that cells can be held to surfaces by long-range electromagnetic forces, which have now been shown to act at thousands of Angstroms separation.

During the sabbatical visit of Professor David Tinker of Toronto we made a survey of the contact forces between protein monomers. We believe we have discerned an unrecognized feature of protein contact: particles that remain in permanent contact touch over surfaces of hydrocarbon. Surfaces between monomers that can separate (dissolve) and rejoin hold together by an intricate matching of positive and negative charges that stud a non-polar surface.

Publications

Cowley, S., Fuller, N., Rand, R. P. and Parsegian, V. A.: Measurement of repulsion between charged phospholipid bilayers. Biochemistry (in press) (1978).

Gingell, D., Parsegian, V. A., Todd, I.: Experimental evidence for long-range attraction between a red cell and a hydrocarbon surface. Nature 268, 767-768 (1977).

Parsegian, V. A., Weiss, G. H. and Schrader, M. E.: Macroscopic continuum model of influence of hydrocarbon contaminant on forces causing wetting of gold by water. J. Coll. Int. Sci. 61 356-361 (1977).

Kiefer, J. E., Parsegian, V. A. and Weiss, G . H.: An easily calculable approximation for the many-body van der Waals attraction between sphere and wall. J. Coll. Int. Sci. 63 161-171 (1978).

Parsegian, V. A.: Considerations in determining the mode of influence of calcium on vesicle membrane interaction. Society for Neuroscience Symposia II. p. 161-171, ed. W . M. Cowan and J. A. Ferrendelli.

Tinker, D. O. and Parsegian, V. A.: Interactions between subunits of protein oligomers. Biophys. J. 21 145a (1978).

McAlister, M., Fuller, N., Rand, R. P., and Parsegian, V. A.: Measurement of surface pressure in and repulsion between approaching phospholipid membranes. Biophys. J. 21 213a (1978).

Lis, L. J., Rand, R. P., and Parsegian, V. A .: Measurement of electrostatic forces between lecithin bilayers charged by divalent cations. Biophys J. 21 145a (1978).

Kiefer, J. E., Parsegian, V. A . and Weiss, G. H.: Some convenient bound and approximations for the many body van der Waals attraction between spheres J. Coll. Int. Sci. (in press).

Brenner, S. L., Parsegian, V . A., and Gingell, D.: The effects of image forces on double-layer interactions. J. Phys. Chem. (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00014-11 PSL

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Theory of Biochemical Separation Techniques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: G. H. Weiss, Chief, Physical Sciences Laboratory
Other: D. A. Yphantis, Professor of Biology
University of Connecticut

COOPERATING UNITS (if any)
None

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
Div. of Computer Research & Technology, NIH, Bethesda, Maryland

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project explores applications of mathematical techniques to biochemical separation techniques such as electrophoresis. Little was done on this project in the past year except to start to look at practical ways of processing data from solutions of heterogeneous proteins.

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(Rev. 10-76)

Only a small amount of effort was expended on this project in the past year pending further experimental work on the theory developed for the acceleration of equilibrium sedimentation experiments. We have started looking at possible ways to process data from equilibrium sedimentation measurements on inhomogeneous proteins.

Keyword Descriptors : Ultracentrifugation, equilibrium, sedimentation, inhomogeneous proteins.

Publications:

Correia, J. J. Weiss, G. H., Yphantis, D. A : An extrapolation method for reducing equilibration times in sedimentation equilibrium experiments. Biophysical Journal 20, 153-168 (1977)

Dishon, M., Weiss, G. H.: When do transient double peaks occur in pH gradient electrophoresis? Analytical Biochemistry 81, 1-9 (1977).