1971

Progress Report No. 7

Biomedical Computer Laboratory

PROGRESS REPORT

No. 7

1 July 1970 - 30 June 1971

Biomedical Computer Laboratory
Washington University School of Medicine
St. Louis, Missouri

BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

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I. INTRODUCTION

This progress report from the Biomedical Computer Laboraty (BCL) summarizes work done during the period from July 1, 1970 through June 30, 1971. The Biomedical Computer Laboratory collaborates with research investigators throughout the Washington University School of Medicine in the application of advanced computer techniques to problems in biology and medicine.

One class of applications requires strong coupling of the computer to its environment. These applications often involve the use of a small computer such as a Laboratory Instrument Computer (LINC) or a Programmed Console (PC). We have pursued these applications by bringing signals from the laboratories to BCL by means of either analog tape recordings or telephone lines and, more frequently, by taking the computers to the laboratory.

A second class of applications requires a computer strongly coupled to its environment and also the advanced information processing capabilities available on large central machines. To meet the demands of this particularly difficult class of applications we have connected most of our laboratory-style computers via telephone lines to the IBM 360/50 at the Washington University Information Processing Center.

A final class of applications requires extensive use of large scale computational services. Many investigators are assisted in their research through the use of generalized numerical, non-numerical, and statistical routines. This work is carried out in part by staff members of BCL, but primarily by members of the Division of Biostatistics under the direction of Dr. Reimut Wette, and the University Computing Facilities whose new director is Dr. Jon Strauss.

The Washington University Computer Laboratories (WUCL) is a federation of computer research activities including the Biomedical Computer Laboratory, the Computer Systems Laboratory, and the Computer Components Laboratory. This federation of laboratories functions through a coordinating committee composed of the three laboratory directors and in addition, R. A. Dammkoehler, C. E. Molnar, and until his resignation in June, 1971 to become Chancellor, W. H. Danforth.

The Computer Systems Laboratory, which is under the direction of Professor W. A. Clark, is active in the design, development and evaluation of a compatible set of "macromodules" from which arbitrarily large, complex, or specialized computer systems can be assembled.

The Computer Components Laboratory, under the direction of Professor W. N. Papian, is a part of the School of Engineering and Applied Science. The Laboratory performs applied research and development work in materials, devices, and circuits for advanced information processing systems.

A National Advisory Panel assists in planning health-related activities and during the past year had the following membership:

H. K. Beecher	Door Professor of Research in Anesthesia	Harvard Medical School
W. H. Danforth	Vice-Chancellor for Medical Affairs	Washington University School of Medicine
K. F. Killam	Professor of Pharmacology	University of California at Davis
F. M. Richards	Professor in Molecular Biophysics and Chemistry	Yale University
R. S. Snider	Professor of Anatomy and Director of Center for Brain Research	University of Rochester

The Advisory Panel meets periodically with the WUCL Coordinating Committee to review developing techniques and to advise upon desirable areas of application.

II. SOURCES OF SUPPORT

During the period covered by this report the primary source of support for the Biomedical Computer Laboratory was a grant from the National Institutes of Health:

RR 00396	A Resource for Biomedical Computing

A training program in Health Care Technology was begun during the year and from it the Laboratory derives partial support:

HS 00074	Technology and Health Care

Collaboration with other investigators often involved work already supported by other grants. Most of this support was from the Public Health Service:

AM 13332	Metabolic Regulation and Inacting Enzyme Systems
CA 04483	Effects of X-Ray on Normal and Malignant Cells
CA 05139	Training in Radiation Therapy Physics and Biology
CA 10435	Clinical Cancer Radiation Therapy Research Center
CA 10926	Use of Heavy Isotopes in Biological Research
EY 00204	Etiology of Reduced Visual Function
GM 01747	Training Program in Radiology (Nuclear Medicine)
GM 13925	Structural Studies on Malate Dehydrogenases
GM 14889	Cyclotron Produced Isotopes in Biology and Medicine
GM 21863	Research Career Development Award
HE 03745	Enzyme Factors Influencing Intravascular Fibrinanalysis
HE 04814	Fibrinolytic Mechanisms
HE 10523	Research Career Development Award
HE 11034	Circulatory Regulation and Myocardial Contractions
HE 11233	Sensitive Radioimmunoassay for Digitalis
HE 12237	Regional Cerebral Functions - Radioatopic Methods
HE 13415	Ca Exchange, Na Competition, and Tension in Atrium

HE 13803	Development of a Trileaflet Aortic Valve Prosthesis
NS 03856	Auditory Communication and its Disorders
NS 05159	Metabolism of Inositols and Inositides
RM 00056	Cooperative Regional Radiation Therapy - Development and Support Program

Atomic Energy Commission:

AT(11-1)-1653	Biologic Consideration in Anatomic Imaging with Radionuclides

Food and Drug Administration:

70-55	Research and Development of Oral Contraceptive Agents and Thromboembolic Complications

Hartford Foundation:

	Cooperative Study in Phase-Shift Balloon Pumping

Jewish Hospital Fund:

850 13051	Action of Bretylium Tosylate on Cardiac Glycoside Induced Arrhythmias

National Science Foundation:

GB 26483X	Enzyme Structure and Function
GB 27437X	X-Ray Structural Studies of Cytoplasmic Malate Dehydrogenases
GK 05563	Investigation of Centrifugal Liquid-Liquid Extraction as a Novel Artificial Lung Design Concept

III. PERSONNEL

EMPLOYEES

Personnel employed by the Biomedical Computer Laboratory during the period covered by this report were:

Director

Jerome R. Cox, Jr., Sc.D.

Assistant Director for Engineering

V. W. Gerth, Jr., M.S.

Administrative Officer

Edward L. MacCordy, M.B.A.*

Associate Professor

Donald L. Snyder, Ph.D., Electrical Engineering

Assistant Professors

William F. Holmes, Ph.D., Biochemistry
Maxine L. Rockoff, Ph.D., Applied Mathematics and Computer Science
Lewis J. Thomas, M.D., Anesthesiology*

Senior Research Fellow

Roger H. Secker-Walker, M.D., since December 15, 1970*

Research Assistants

Robert J. Arnzen, Ph.D*
James M. Baker, B.S.
Carole Ann Benbassat, B.S., since October 8, 1970*
Philip S. Berger, M.S.
G. James Blaine, M.S.
Andrew L. Bodicky, B.S.
Kenneth W. Clark, M.S.
Carol S. Coble, A.B.
Robert H. Greenfield, M.S., since August 1, 1970
Ronald W. Hagen, M.S.*
Rexford L. Hill, III, M.S.
Sung-Cheng Huang, M.S.
Akihiro Ichijo, M.S.
Stanislav Jedlicka, M.S., since September 1, 1970
Kenneth B. Larson, Ph.D.
Monte D. Lien, M.S.
Gerald R. Little, Ph.D., since July 1, 1970*

Michael D. McDonald, B.S.
Joanne Markham, B.A.*
Nizar A. Mullani, B.S.
Floyd M. Nolle, M.S.
Robert H. Pape, B.S., since September 1, 1970
James M. Pexa, M.S.
Carl F. Pieper, B.S., since September 1, 1970
Bruce F. Spenner, M.S.
Elizabeth Van Patten, B.A.

Technical Assistants

Betty J. Greenwood
James B. Minard, since September 5, 1970
Emil D. Scheifler

Programming Assistants

William V. Glenn, Jr., M.D.
John A. Parker, B.A.
Robert N. Tatum, since November 13, 1970

Engineering Assistant

H. Dieter Ambos

Electronics Technicians

Charles R. Buerke
Christopher R. Fraction
Kenneth L. Kunkelmann

Machinists

George C. W. Meyer*
Michael Nibaldo, since March 29, 1971

Librarian

Allie Allmon, B.S.*

Laboratory Assistants

Fritz Kunze, since September 16, 1970
Allen Sanders*

Business Manager

Virginia M. Bixon, B.S.

Secretaries

Viviane D. McKay, since August 3, 1970*
Wanda J. Meek
Linda S. Russo
Sandra Sfondouris

*Indicates at least 50% of the individual's effort is supported by another laboratory or department.

Changes in Personnel

During the period covered by this report the following personnel resigned or completed their work at the laboratory:

William V. Glenn, Jr., terminated February 28, 1971
Steven D. Iceland, terminated August 31, 1970
Akihiro Ichijo, terminated May 31, 1971
Gerald R. Little, terminated August 31, 1970
George C. W. Meyer, terminated January 31, 1971
Robert H. Pape, terminated September 30, 1970
Allen Sanders, terminated August 31, 1970

Summer Personnel

In addition, the following people worked at the laboratory for brief periods:

Steven D. Iceland, B.A., Summer, 1970
Ronald Inselberg, Summer, 1971
Jeffrey F. Painter, Summer, 1971
Alan J. Tiefenbrunn, Summer, 1971
Geoffrey M. Waldron, Summer, 1970
Louis J. West, Summer, 1970, 1971

RESEARCH COLLABORATORS

During the period covered by this report the following investigators from other laboratories, departments, or institutions, collaborated with BCL staff members on problems of joint interest:

Washington University

U. T. Aker, M.D., Medicine
W. L. Anderson, B.A., Radiology
J. Armstrong, M.D., Radiology
R. M. Arthur, Ph.D., Electrical Engineering
W. E. Ball, D.Sc., Applied Mathematics and Computer Science
L. J. Banaszak, Ph.D., Physiology and Biophysics

D. J. Bates, A.B., Biochemistry
R. A. Beauchamp, Anesthesiology
L. Broch, B.S., Opthalmology
C. C. Carter, M.D., Neurology
T. J. Cicero, Ph.D., Psychiatry
R. E. Clark, M.D., Surgery
W. A. Clark, B.A., Computer Systems Laboratory
J. A. Collins, M.D., Surgery
R. A. Cook, Ph.D., Computing Facilities
A. J. Demidecki, M.S., Radiology
D. C. DeVivo, M.D., Pediatrics and Neurology
G. R. Drysdale, Ph.D., Biochemistry
J. O. Eichling, Ph.D., Radiology
J. M. Enoch, Ph.D., Opthlmology
N. J. Falvey, B.S., Information Processing Center
A. Feldman, Ph.D., Radiology
A. P. Fletcher, M.D., Medicine
N. A. Fletcher, Ph.D., Medicine
H. Fotenos, Radiology
M. A. Franklin, Ph.D., Electrical Engineering
C. Frieden, Ph.D.,
T. L. Gallagher, Sc.D., Information Processing Center
R. Glenn, Radiology
S. Goldring, M.D., Neurosurgery
J. Hecht, A.B. Radiology
R. M. Hochmuth, Ph.D., Chemical Engineering
W. H. Holland, A.B., Psychiatry
P. L. Jacobson, Medicine
L. Jarett, M.D. Pathology
G. C. Johns, B.S., Computer Systems Laboratory
L. I. Kahn, M.D., Preventive Medicine
R. E. Kleiger, M.D., Medicine
R. M. Kline, Ph.D., Electrical Engineering
R. H. Kornfeld, Ph.D., Medicine
S. A. Kornfeld, M.D., Medicine
S. Lang, Ph.D., Physiology and Biophysics
M. D. Loberg, B.S., Radiology
F. S. Mathews, Ph.D., Physiology and Biophysics
J. Metzger, M.A., Radiology
B. D. Milder, B.S., Opthalmology
C. E. Molnar, Sc.D., Computer Systems Laboratory
G. C. Oliver, Jr., M.D., Medicine
G. T. Perkoff, M.D., Preventive Medicine
P. E. Peters, M.D., Radiology
R. R. Pfeiffer, Ph.D., Electrical Engineering
M. D. Phelps, Ph.D., Radiology
E. J. Potchen, M.D., Radiology
W. E. Powers, M.D., Radiology

G. W. Roberts, Sc.D., Chemical Engineering
S. D. Rockoff, M.D., Radiology
R. E. Roeder, M.D., Medicine
A. Roos, M.D., Anesthesiology
R. S. Rosenfeld, M.D., Medicine
L. Roy, Medicine
J. H. Scandrett, Ph.D., Physics
W. R. Sherman, Ph.D., Psychiatry
B. A. Siegel, M.D., Radiology
S. Smith, M.S., Applied Mathematics and Computer Science
E. E. Spaeth, Ph.D., Chemical Engineering
M. Straatmann, B.S., Radiology
J. S. Strauss, Ph.D., Computing Facilities
S. P. Sutera, Ph.D., Mechanical Engineering
M. M. Ter-Pogossian, Ph.D., Radiology
L. J. Tolmach, Ph.D., Radiology
B. Walz, M.D., Radiology
D. F. Wann, D.Sc., Electrical Engineering
M. J. Welch, Ph.D., Radiology
C. S. Weldon, M.D., Surgery
M. Werner, M.D., Pathology
R. Wette, D.Sc., Biostatistics
M. A. Whitney, Ph.D., Preventive Medicine
G. A. Wolff, M.D., Medicine
A. R. Zacher, Ph.D., Physics

<u>M. D. Anderson Hospital and Tumor Institute, Houston, Texas</u>

R. J. Shalek, Ph.D.
M. Stovall, B.S.

<u>Barnes Hospital, St. Louis, Missouri</u>

K. F. Bemberg

<u>Central Institute for the Deaf, St. Louis, Missouri</u>

L. L. Elliot, Ph.D.
D. H. Eldredge, M.D.
I. J. Hirsh, Ph.D.
R. F. Kimach
J. D. Miller, Ph.D.
D. A. Ronken, Ph.D.
C. S. Watson, Ph.D.

George Washington University, Washington D. C.

F. Siegel, M.D.
J. R. Whiteman, M.D.

Karolinska Institute, Stockholm, Sweden

C. G. Hammar, Ph.D
R. Hessling, B.S.
B. Holmstedt, M.D.
A. Linnarsson, B.S.
L. Pierrou, B.S.

Methodist Hospital, Houston, Texas

D. Brooks, M.D.
M. E. DeBakey, M.D.
C. J. Flynn, M.D.
D. H. Glaeser, Sc.D.
S. M. Rhode

National Cancer Institute, Bethesda, Maryland

F. Faw, B.S.
D. W. Glenn, M.S.
R. Johnson, M.D.

New England Medical Center, Boston, Massachusetts

P. W. Neurath, D.Sc.
D. A. Low, A.B.

Ontario Cancer Institute, Toronto, Canada

J. R. Cunningham, Ph.D.
W. D. Rider, M.D.

Royal Marsden Hospital, Institute of Cancer Research, Surrey, England

R. E. Bentley, Ph.D.
J. Milan, M.S.

St. Lukes Hospital, St. Louis, Missouri

W. V. Glenn, M.D.

Stanford University, Stanford, California

C. J. Karzmark, M.D.
D. C. Rust

Temple University, Philadelphia, Pennsylvania

K. C. Tsien, M.A.
D. J. Wright, Ph.D.

University of Chicago, Chicago, Illinois

H. A. Fozzard, M.D.
B. E. Oppenheim, M.D.

University Hospital, London, England

J. S. Clifton, M.Sc.

University of Saskatchewan, Saskatoon, Canada

G. T. Andrews, B.Sc.
D. Howe, M.A.

Yale University, New Haven, Connecticut

A. L. Finn, M.D.

Previous years have seen occasional collaborative efforts with various computer firms and equipment manufacturers. This year has seen a substantial increase in this kind of activity. Projects of joint interest have been continued or begun with:

Artronix Instrumentation, Inc., Brentwood, Missouri - A radiation treatment planning system

Digital Equipment Corporation, Maynard, Massachusetts - Design of a computer interface for gamma-ray cameras

Mennen-Greatbatch Electronics, Inc., Clarence, New York - An ECG rhythm monitoring system

IV. PHYSICAL RESOURCES

On April 15, 1964, the Biomedical Computer Laboratory was formed and the original staff moved into 5,515 square feet (gross) of laboratory space at 700 South Euclid Avenue, just across the street from the main building of the Washington University School of Medicine. Equipment then available for laboratory applications of digital computers included a LINC (Laboratory INstrument Computer). This small stored-program computer has been designed specifically for use in biology and medical laboratories where there is a requirement for strong coupling between the computer, the investigator, and other experimental equipment. Since that time some twelve LINC's and five PDP-12's a newer implementation of the LINC, have been added to the resources of the Washington University medical community.

In 1966 the Programmed Console was designed at BCL to function as a combined stored-program digital computer and remote display console for the IBM 360/50 installed during May, 1966, at the Washington University Information Processing Center. BCL's computational facilities now include three specialized Programmed Consoles built at the laboratory. In addition, thirteen Programmed Consoles have been built by SPEAR, Inc., from plans and specifications developed at BCL. Of these, six are now being evaluated under an NIH sponsored program as an aid to radiation treatment planning at radiology centers in Stanford, California; Bethesda, Maryland; Houston, Texas; Boston, Massachusetts; Philadelphia, Pennsylvania; St. Louis, Missouri; and Toronto, Canada. Two Programmed Consoles manufactured by SPEAR, Inc. are in use in other projects at BCL.

Other laboratory facilities include a data transmission distribution system, a well-stocked electronics shop, a large inventory of electronic and computer test equipment, a variety of digital system modules, and both analog and digital tape recorders.

During the past six years the laboratory space has been increased by 1526 square feet in the basement, 2762 square feet on the ground floor and 3171 square feet on the second floor of 700 South Euclid, and by 3463 square feet on the second floor and 1257 square feet of the basement of the building just south of the original space. Facilities for computational applications, laboratories, staff offices and a WUCL research library are provided in these acquired spaces. Direct communications with the IBM 360/50 at the Washington University Information Processing Center is provided via phone lines, Programmed Consoles and LINC's.

On October 1, 1969, an on-line computer monitoring system was installed by BCL in the Cardiac Care Unit of the Barnes Hospital complex. The computer equipment is housed in 360 square fee of specially designed space within the unit. Key BCL staff members occupy 260 square feet of office space nearby.

V. RESEARCH PROJECTS

Summary

Since the organization of the Biomedical Computer Laboratory in April, 1964 the spectrum of research projects has grown considerably. This year it seems appropriate to initiate a brief summary report to aid the reader and to place in a broader context the individual reports which follow.

The major goal of the Laboratory is the application of computer techniques to problems in medicine and biology. This often requires work in areas stretching from basic physiology through mathematical models, to the nuts, bolts, integrated circuits and connectors of hardware design. Our orientation is interdisciplinary with the recognition that effective communication for workers with differing backgrounds comes only through extended collaboration and mutual respect. The Laboratory's research program has been organized into several major project areas with many of the Laboratory staff grouped into teams whose interests concentrate in one of these project areas.

A. Radiation Treatment Planning. This oldest of the Laboratory's major projects has moved to commercial implementation. Our recent activity has concentrated on user liaison, documentation and maintenance of application programs. Development work by the Laboratory, has now been built on by two computer manufacturers. This development work was essential to the solution of the treatment planning problem, but difficult because of limited sales potential to support the manufacturer's research and development budgets. Nevertheless, the problem was an important one to the few hundred treatment centers in the nation and demonstrates the pathfinder role the Laboratory can play for industry.

B. Electrocardiographic Rhythm Monitoring. The opening of the Barnes Coronary Care Unit in October, 1969 marked a turning point for this work. Clinical application of the rhythm monitoring algorithms developed over the previous years became a reality. An evaluation of the performance of Argus (Arrhythmia Guard System) was begun last year and reported in the fall. This rigorously controlled study showed detection by Argus of 78% of the premature ventricular contractions with 0.4% false positives. These results were obtained on a group of 34 patients undergoing active therapy for ventricular arrhythmias and represent a kind of "worst case" for rhythm complications.

With this evidence of reasonable performance of Argus an experiment to evaluate the clinical impact has begun. Preliminary results have been encouraging and a commercial version of Argus is under development.

Recent attention to the investigation of the causes of sudden cardiac death has helped to identify the role that can be played by a high speed version of Argus. A study has been proposed involving the high speed analysis of about 20,000 hours of tape recorded data from 100 ambulatory subjects at risk from life threatening arrhythmias.

C. Regional Tracer Kinetics. The connection of gamma-ray cameras and digital computers in recent years has been stimulated by the anticipation of a variety of new diagnostic procedures utilizing radio pharmaceuticals and with broad importance to clinical medicine. The requirements for data acquisition and analysis in the application of these diagnostic procedures are stringent and demand the use of computational tools. To increase our understanding of clinical problems for which the techniques of regional tracer kinetics apply and to provide a forum for some of the computational and mathematical tools that we have developed over the last three years a five day workshop was held at Washington University in January, 1971. The proceedings of the Workshop are being published in two volumes, the first already out, the second to be completed in the fall. The first volume attempts to present some of the underlying technical, physical and mathematical foundations of systems for studying regional tracer kinetics. Reaction to it has been enthusiastic both in its original form as lecture notes for the Workshop and as it subsequently has appeared.

One of the important developments presented at the Workshop was a system of programs and an interface between a gamma-ray camera and a Digital Equipment PDP-12 computer. This interface is likely to form the basis for a commercial system to be available by 1972.

Since the Workshop steady progress has been made toward the implementation of techniques for estimating such diverse physiological quantities as kidney blood flow, lung ventilation and perfusion, cardiac ejection fraction, gastric emptying rate and regional lung water.

D. Monitoring the Critically Ill. The design of the Surgical Intensive Care Unit (SICU) has been completed and renovations are scheduled to be done in the fall. Equipment for digital communications and data display have been added to the transducer, signal-conditioning and computer portions of the system. The digital communications will allow high speed transmission of data between the SICU, the Coronary Care Unit and the General Clinical Research Center.

As a preliminary step in this program a digital computer system had been installed in the cardiac catheterization laboratory to help with the acquisition and processing of electrocardiographic and hemodynamic data. This supplementary project has been helpful in the design of the SICU because of the experience gained with transducers and signal analysis techniques. In addition, the system appears to be enormously useful in its own right as an aid to the cardiologist. Conversations with manufacturers have begun that may lead to the commercial availability of the next version of this catheterization laboratory system. Thus, in future reports, work on this system will be described in a section of its own.

E. Collaborative Data Processing. Usage of the network of small computers linked to the University's IBM 360/50 via telephone lines continues to expand. Work in Regional Tracer Kinetics and Radiation Treatment Planning generates the heaviest use, but many other activities take advantage of the ready availability of the extended computing power at the University's central facilities. Work this year has concentrated on increasing the capability and reliability of the network. Expansion of the system from ten to at least twenty stations is planned for the coming year.

F. Other applications of computers. A number of projects do not fit the previous five categories, but are pursued because of their own special interest or because they may develop into one of the Laboratory's major areas of activity. The application of computers in biochemistry has flowered in the past year so that it will be reported separately next year. In particular, the use of a computer with a mass spectrometer for control, data acquisition, and data processing has developed to the state that programs developed by us are being used by five other laboratories on similar computer systems. Techniques for analyzing picogram quantities of substances with unknown compositions are under development.

Noteworthy, among the other projects is the development of an Automatic Drug Injection System (AUDRI) for the control of tissue culture experiments with up to 48 pairs of petri dishes.

Individual Projects

A-1. Commercial Availability of the Radiation Treatment Planning System

Personnel: V. W. Gerth, Jr., BCL
J. R. Cox, Jr., BCL

Support: RR 00396
Washington University

In October, 1970, Spear, Inc. announced the discontinuance of their production of commercial versions of the Programmed Console. They had provided the machines used in the evaluation of the Radiation Treatment Planning System (see PR 6, A-5) as well as machines ordered by institutions not in the evaluation program.

Upon learning of this development, another firm, Artronix, Inc. of St. Louis, Missouri indicated an interest in developing a new version of the Programmed Console as a commercial product. Artronix was already experienced in producing instruments used in radiology departments and felt that the addition of a computer-aided Radiation Treatment Planning System would complement their existing product line.

BCL provided the logic drawings for the original versions of the PC produced in the laboratory as had been done with Spear and some other firms. Artronix then designed and developed a new version which is superior to the previous versions in many respects but maintains near-total software compatibility.

The major new features include the addition of LINC-tape as the standard mass storage device, a convenient approach to memory extension, a flexible I-O bus structure including multi-level hardware priority interrupt and DMA with hardware priority, and a memory cycle time of 1.0 microsecond.

Artronix has converted the datamaster-oriented Radiation Treatment Planning Programs for tape operation and has indicated a commitment to continued support and new development of application oriented software. The first systems are in operation and deliveries to customers are expected shortly.

In 1968, Dr. Roy E. Bentley returned to the Royal Marsden Hospital near London after spending a year at BCL (see PR 4). There he began the development of a new version of the Radiation Treatment Planning System for a Digital

Equipment Corporation PDP-8 with 8K of memory, extended arithmetic hardware, and a dual tape transport. This work was carried out by Mr. Jonathan Milan with assistance from Digital Equipment Corporation. A version of the system, RAD-8 was announced by DEC last year and several systems have been installed. Since then Bentley and Milan have further improved the Royal Marsden version of the system, decreasing substantially the calculation time for isodoses. The incorporation of tape in the system increases the convenience substantially and the shortened calculations are comparable in speed to the PC version.

Other radiation treatment planning systems like the PC, but using a DEC PDP-12 are under development at Vanderbilt University and at San Francisco Medical Center. These developments have both benefited from the work done at BCL and at the Royal Marsden.

A-2. Annotation of Superimpose Beams Program

Personnel: B. J. Greenwood, BCL
W. F. Holmes, BCL

Support: RR 00396
Washington University

To enable program modification of Superimpose Beams, documentation was compiled which included the following data: an annotated listing; descriptions of subprograms, subroutines, program options and option subroutines plus lists for each of their index and image registers, tags and data areas; data area descriptions and formats; overall subprogram flow charts; detailed subroutine and subprogram flow charts; memory maps; charts of index and image register tags, their contents, and where they are used; subroutine calling sequences; and descriptions of the mathematical methods used throughout the program.

A-3. PC Planner's Press

Personnel: B. J. Greenwood, BCL

Support: RR 00396
Washington University

Publication of the PC Planner's Press, an aid to PC users, continued with an issue covering the following topics:

1. DIALUP Equipment Information.

2. Additions to the list of Monographs pertaining to the PC.

3. Request for descriptions of User digitized beams to enable compilation of a master list of beam data available.

4. Request for descriptions of User written PC programs which will be published in future issues of the newsletter.

5. Announcement of the discontinuance of Spear's PC project.

6. Introduction of Artronix, the manufacturer of the new PC 1200.

7. Announcement of the availability of design modification necessary to implement the use of a Teletype as a remote keyboard for the PC.

8. Summary of the July 16, 1970 PC User's meeting in Washington, D.C.

A-4. P.C. Movie

Personnel: B. J. Greenwood, BCL
V. W. Gerth, Jr., BCL

Support: RR 00396
Washington University

The story of the need for, development and operation of the Programmed Console was put onto film in the form of a 16 mm color, sound movie, "This is the PC." Filmed at BCL and Mallinckrodt Institute of Radiology, using staff from both areas as actors, the movie explains why the PC was needed and how it evolved. It demonstrates how the PC is used by doctors and their technicians to rapidly and accurately develop radiation treatment plans for their cancer patients. A fairly detailed explanation follows, showing an operator manipulating the PC and its accessories through the major steps required in the development of a treatment plan. Finally, the use of the PC is explained and shown as applied to the Federal Regional Medical Program in operation at Mallinckrodt where isodoses are calculated and radiation plans are checked for twenty hospitals in a two-state area.

A-5. Revision of Instruction Manuals for Radiation Treatment Planning

Personnel: B. J. Greenwood, BCL
W. F. Holmes, BCL

Support: RR 00396
Washington University

Final revision was completed of the following instruction manuals to standardize their format; incorporate program revision, deletions and additions, and provide more easily understood operating procedures for each program used in radiation treatment planning.

54 Enter Patient Contour

65 Radiation Treatment Planning

81 DMUTIL

96 CONSTANT

100 Datamaster Operating Instructions

105 Enter Doses

A-6. A Computer Controlled Dose Plotter

Personnel: A. Feldman, Ph.D., Radiology
A. L. Bodicky, BCL
C. Benbassat, BCL
R. Glenn, Radiology

Support: RR 00396
CA 10435
RM 00056

Previous work has been described in PR 6, A-6. During the past year the effort has consisted of careful examination of the program for operating the dose distribution acquisition system. In particular, attention has been given to programming changes to overcome problems of detector response and noise. Consideration is being given to the special problem of obtaining dose distributions from machines such as linear accelerators, where the radiation output in general cannot be held steady. Some design changes of the mechanical system are under consideration.

A-7. RAPID - Radioactive Point Implant Dosimetry

Personnel: E. Van Patten, BCL
W. L. Anderson, B.A., Radiology

Support: RR 00396
CA 10435

All of the improvements to the PC portion of the RAPID program as detailed in PR 6, A-1 (CalComp output, rho-theta input, improved editing, improved recovery procedures after 360 or transmission failure, and provision to save data or output) have been completed. The improved version is now in regular use.

A-8. Implementation of Memorial Treatment Planning Program on the IBM 360/50

Personnel: C. Benbassat, BCL
A. Feldman, Ph.D., Radiology
B. Walz, M.D., Radiology

Support: RR 00396
CA 05139

Two versions of the Memorial Treatment Planning Program were received from Memorial Hospital, one version to be used for Cobalt-60 treatments and the other for treatments by a 4 MeV linear accelerator. The two versions were combined into one program to be used for both types of treatment. Furthermore other changes were needed because of the differences between the Fortran programming language used on the computer at Memorial Hospital and that used on the Washington University IBM 360/50. The output of the program has been checked and found to be accurate for some test executions.

B-1. Argus Processing Algorithms - Development and Evaluation

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Support: RR 00396
HE 11034
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The Argus Cycle processor algorithms for the formation of families of QRS complexes and for the classification of each QRS as normal, abnormal, PVC, etc., (see PR 6, B-2), have been recently described[1]. A recent technical evaluation (see PR 6, B-4) of Argus' ability to detect PVC's has also been concluded and reported[2]. A variety of changes have been made in the Argus software relating to improved operational characteristics, but the major developmental efforts have been related to off-line formulation of algorithms based primarily on the large variety of documented data collected in the recent evaluation of Argus.

One area of development has concerned generalization of the present Argus algorithm for clustering families of normal QRS complexes to clustering of other groups of families for purposes such as identification of multifocal PVC's. Another area involves modification of the current cycle data stream for more efficient coding, but with improved reconstruction capability. A third investigation has centered on the possibilities of refinements in the Primitive algorithm (see B-15). Other algorithms have been considered for automatic adjustment by Argus of PVC alarm limit settings, automatic signal amplitude adjustment and the addition of signal-in-noise detection techniques with automatic switch-over during periods of artifact.

(1) F. M. Nolle and K. W. Clark, "Detection of Premature Ventricular Contractions Using an Algorithm for Cataloging QRS Complexes," Proceedings of the San Diego Biomedical Symposium (in press).

(2) G. C. Oliver, F. M. Nolle, G. A. Wolff, J. R. Cox, Jr. and H. D. Ambos, "Detection of Premature Ventricular Contractions with a Clinical System for Monitoring Electrocardiographic Rhythms," to be published in Computers and Biomedical Research.

B-2. A Data Storage System for Argus

Personnel: F. M. Nolle, BCL
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G. J. Blaine, BCL
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Support: RR 00396

A disc-oriented system has been constructed for mass data storage and retrieval to aid on-line evaluation of the Argus algorithms. A fixed-head, 64-track, 6.4 megabit disc (Data Disc 7206) was interfaced to an 8K, 1.6 μs processor (DEC PDP-8L) via the single-cycle data break channel. Each disc track contains 32 blocks of 256 thirteen-bit words (twelve data bits plus parity), providing a total disc capacity of 2048 blocks, the equivalent of four standard LINC tapes. An IOT instruction initiates reading or writing of one block of disc data whose address is specified by the contents of the PDP-8 accumulator ($0\text{-}3777_8$). A separate IOT instruction is used to set the initial data transfer core location (modulo 400_8). A program interrupt is generated upon completion of disc transfer and additional IOT instructions test for parity error and transfer completion. Worst case access time for a block of data is 33.3 ms and the transfer time is 1,024 μs. The maximum attainable data transfer rate is 16 blocks in 33.3 ms and occurs when requested block addresses are sequentially increased by two (modulo 40_8). In order to allow concurrent processing and disc transfer, the interface contains a four-word circular buffer between disc and core memory. This buffer allows operation under worst case conditions when a data break request occurs shortly after the beginning of an IOT instruction which is followed by a memory reference instruction with indirect addressing.

Three identical communication ports lead to the LINC-8 and the two prototype PC's which are presently operating as patient computers. Each port allows concurrent input and output of twelve-bit parallel data or command words under program control. Program interrupt logic may be selectively enabled or disabled for each input path and each output path. Since the data storage system has now broken the pathways which formerly existed between the LINC-8 and the PC's (see PR 6, B-10), backup operating capability is provided by a patch panel which allows one or both of the former LINC-8 to PC pathways to bypass the data storage system.

B-3. Data Storage System Software

Personnel: K. W. Clark, BCL

Support: RR 00396

Operational software for the Argus data storage system (see B-2) has been designed for on-line, around the clock performance. The basic data storage system software concept is to accumulate on disc long segments of selected Argus data streams emanating from the patient computers. Thus, precise sequences of events may be reconstructed minutes or even many hours after they have disappeared from the very short-lived storage areas in the PC's, allowing systematic data collection for evaluation studies. The system also provides hitherto unattainable capability to examine in detail Argus' measurements on waveforms which are encountered during frequent spot checking of Argus for quality control purposes.

The following general guidelines have been followed in developing operational data storage system programs. All data collected from the PC's is obtained via the PC/PDP-8L communication ports using the SNOOPI technique (see B-11). PC data is stored in circular buffer areas on disc with the newest data overlaying the oldest data. PC data storage areas are restricted to disc addresses 2000_8 through 3777_8 (the equivalent of two classic LINC tapes). The LINC-8/PDP-8L communication port is used upon request by the LINC-8 (a) to transfer a block of data to the LINC-8 from any disc address, (b) to transfer a block of data from the LINC-8 to any disc address from zero through 1777_8, and (c) to allow the LINC-8 use of the SNOOPI technique to access data in the memory of either PC as well as lower core in the PDP-8L.

The present operation of the data storage system is concerned with data collection for the clinical impact study now in progress (see B-6). The single data stream produced consists of (a) Cycle processor data for each ventricular event (the family name, pathology, PVC classification, occurrence time), (b) a short segment of Aztec data encompassing the first member of each new QRS family, (c) summary data at the end of each minute (heart rate, PVC rate, data loss, alarm limit settings and other status information), and (d) nature and time of occurrence of alarms. This single data stream occupies the entire PC half of the disc since only one PC is being used for the clinical impact study (see B-6), and the eight to twelve hours of data in the buffer allow relatively infrequent copying to LINC tape.

A data storage system program which had been developed prior to the current program allowed storage of the higher rate Aztec and Primitive data streams as well as Cycle data. Buffer sizes for each data stream were selected so that the most recent 15 minutes (approximately) of each data stream from both PC's was available. Occurrence times for Aztec and Primitive were inserted at the start of each data block to allow synchronized reconstruction of the three data streams.

In addition to the operational software, special programs have been developed to test the reliability of the disc system and to aid in maintenance. These tests have indicated that the disc meets the quoted specification of one recoverable read error in 10^{10} bits although the error rate may be transiently much higher for a few hours after power turn on.

B-4. A Commercial Version of Argus

Personnel: F. M. Nolle, BCL

Support: Washington University

The supplier of the conventional monitoring equipment in the Barnes Hospital Coronary Care Unit has undertaken an effort to develop as a part of its product line a computer-based, multiple-patient arrhythmia monitoring system using the Argus algorithms. Consultation with their personnel regarding the minute details of the algorithms has been in progress and it is expected the first system produced will be tested and installed in the Barnes Hospital Coronary Care Unit.

B-5. Clinical Research Using Argus

Personnel: G. A. Wolff, M.D., Medicine
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Patients in several diagnostic categories frequently pose difficult problems in the analysis and treatment of ventricular extrasystoles. The premature ventricular contraction is currently the object of intensive study by cardiologists and cardiac physiologists. This phenomenon, and the cardiac arrhythmias derived from it, are central to the problem of sudden cardiac death, mortality in the acute myocardial infarction, and morbidity in chronic coronary artery disease, rheumatic heart disease, cardiomyopathy, and such diverse syndromes as the systolic click-late systolic murmur syndrome.

Diagnostic efforts for patients in many of these categories must include the description of a pattern of occurrence and causation of the ectopic beats. Therapeutic efforts must be evaluated by noting the quantitative change in ectopic beats produced by any therapy. The objective of the present research project is to apply the Argus system to patients who suffer from frequent disabling ventricular extrasystoles which have been refractory to conventional diagnosis and therapy.

Four patients have been monitored to date. Two of these have been on the clinical research unit of the Washington University School of Medicine, one on the regular divisions of Barnes Hospital and one has come to the Barnes Hospital Coronary Care Unit for out-patient visits. The monitored electrocardiographic data have been analyzed on-line by the Argus system. Numbers of ventricular extrasystoles appearing at rest and under various physiologic and pharmacologic stresses have been tabulated. Changes in trends and in absolute numbers of ventricular extrasystoles have then been recorded as specific therapies have been given.

Treatment regimens have been constructed using the data gathered.

B-6. Evaluation of Clinical Impact of Argus

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A systematic study is in progress to evaluate the impact of Argus on patient care in the Barnes Hospital Coronary Care Unit. This study tests the hypothesis that information provided by the Argus system is of clinical importance to patients recovering from an acute myocardial infarction. Patients admitted to the study are recent admissions (within 12 hours) who have an admitting diagnosis of definite or possible myocardial infarction. One group of patients studied will be monitored by Argus and information regarding arrhythmias will be provided to the medical personnel in the usual fashion. A second group will be monitored by Argus, but the results of Argus' analysis will not be made available to the staff. The conventional Coronary Care Unit equipment will continue to be used for monitoring both groups.

Although Argus at present recognizes only ventricular arrhythmias, it has the advantage of being able to constantly check an ECG twenty-four hours a day. This should be especially important when the staffing/patient ratio is low or when much activity is centered around one or two patients, e.g., during resuscitation procedure. Therefore, a record is being kept of staffing, all special procedures, and patient census on an hourly basis. The complete medical record of each patient studied is being reviewed and saved for future reference. Argus generated trend data and ECG alarm strips are collected and a modified Cycle data stream (see B-3) is being saved on LINC tape for the entire period of the study. Also, a continuous record of each patient's ECG is saved on analog tape for the period he is monitored by Argus.

The impact of Argus upon patient care will be evaluated by searching for differences between the two groups in mortality, incidence of primary arrhythmias, numbers of resuscitations required, lidocaine dosage, and time of treatment relative to time of onset of a serious arrhythmia.

B-7. Processing Electrocardiograms of Ambulatory Patients

Personnel: R. E. Kleiger, M.D., Department of Medicine, Jewish Hospital

Support: RR 00396

The Holter-Avionics unit is a light weight, portable tape unit capable of recording the electrocardiogram of ambulatory patients. The usual analysis of the tapes is performed by high speed manual scanning with the electrocardioscanner which allows detection of arrhythmias and ST segment abnormalities. The data obtained, however, is qualitative since the number of abnormal events cannot readily be determined by the usual scanning method. Several groups of patients with high incidence of arrhythmias have been monitored by us. These include patients with click-systolic murmur syndrome, patients with severe pulmonary disease and arterial hypoxemia, and patients with coronary artery disease. Meaningful analysis of these patients requires quantitative data. Six patients with click-systolic murmur syndrome have had their tapes analyzed in real time by phone line connection to the Argus system at the Barnes Coronary Care Unit. The computer analysis has found events such as short runs of PVC's and multifocal PVC's which were not seen on manual scanning, has quantitated the total number of premature ventricular contractions, and has given a count of the average number of PVC's per minute, parameters impossible to obtain with manual scanning.

B-8. Collaboration with Baylor College of Medicine in the Development of an ECG Processing System

Personnel: F. M. Nolle, BCL
J. R. Cox, Jr., BCL

Support: RR 00396

Extensive consultation has continued with our colleague, Dr. D. H. Glaeser, and other personnel at the Baylor College of Medicine regarding the details of the Argus algorithms. Their translation of these algorithms to the PDP-12 has been an important factor in the patient monitoring system now in operation at the Methodist Hospital Surgical Intensive Care Unit. During the course of this consultation the foundation was layed for the recently completed documentation of the current Cycle processor algorithms (see B-1). In addition, independent implementation of the algorithms has helped to clarify several subtle points.

B-9. Construction and Testing of a Macromodular AZTEC Processor

Personnel: F. M. Nolle, BCL
J. R. Cox, Jr., BCL
C. F. Pieper, BCL

Support: RR 00396

We have recently become interested in developing special versions of the Argus system for analysis of tape recorded ECG's played back at 60 times real time. Since this requires processing new samples every 33 microseconds and since the Aztec algorithm in our present machines (Prototype Programmed Consoles with 3.1 μs memory cycle time) takes an average processing time per sample of about 300 μs and a worst-case time of about 600 μs, the Aztec algorithm must clearly be implemented with special purpose hardware. Accordingly, we constructed a Macromodular Aztec processor to test the feasibility of the high speed analysis system.

A μLINC-300 was used to send samples from LINC tape to the Macromodular Aztec processor and to display both the sampled data and the Aztec data returned by the processor. The performance was completely satisfactory and measurements of processing time per sample showed an average of about 5 μs and a worst-case of about 10 μs, providing ample speed for 60 times real-time operation.

B-10. Construction and Testing of a Macromodular QRS Detector

Personnel: C. F. Pieper, BCL
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An algorithm developed at George Washington University for QRS detection and boundary determination based on analysis of the first derivative of the ECG was implemented with macromodules. Procedures for testing the Macromodular processor were similar to those described in B-9 with the display modified to indicate QRS boundaries. With a wide variety of clinical waveforms available the hardware implementation was found well suited for experimental optimization of program parameters. Elapsed time from flow chart to a working system was two days.

B-11. Support Software for Argus

Personnel: K. W. Clark, BCL
F. M. Nolle, BCL
L. J. West, BCL

Support: RR 00396

A large number of programs have been written for the LINC-8 to support the investigations connected with Argus. Many of these programs require diverse types of data originating in the Argus Patient Computers. It was recognized quite early that the operational PC programs could not be modified for every new investigation requiring different data streams. Moreover, the LINC-8/PC communications paths (see B-3) would be inundated with information if all conceivable data were routinely sent out by the PC's. Thus, a simple communications protocol has been devised and has been found adequate for the vast majority of programs requiring data collection. The SNOOPI (Send Needed Output On Periodic Interrupt) communication protocol places the information gathering burden on the data collection device. Under present operation, the snooper (e.g., the LINC-8) sends to the snoopee (e.g., a PC) the core memory address of any desired datum which the snoopee then sends to the snooper, thus completing the process. The SNOOPI technique has also been a useful debugging aid for on-line observation of the operation of the Patient Computer and Data Storage System algorithms.

LINC-8 programs have been written for hard-copy plots or print-out of the trend data information (PVC rate, heart rate, data loss) and the alarm history information displayed by the PC's.

Other programs allow instant replay displays, plots, and print-out of electrocardiographic data reconstructed from various combinations of Aztec, Primitive, and Cycle data stored in the Data Storage System or on LINC tape. Programs for studying the Argus process of QRS family formation allow observation of the family clusters for both on-line and off-line data. To aid the operation of these and many other programs, the Progofop I-O routine in the LINC-8 has been modified to address sections of the Data Storage System disc as LINC tape units.

B-12. Argus Hardware Modifications and Additions

Personnel: H. D. Ambos, BCL

Support: RR 00396

Chart Recorders. Two single channel Mennen-Greatbatch ECG chart recorders were installed in the Coronary Care Unit (CCU) computer room in parallel with the existing nurse station chart recorders. This allows the recording of computer initiated alarm strips regardless of switch settings at the nurse stations.

TV Monitors. Two seven-inch Sony TV monitors were installed at the acute and graduate nurse stations in specially designed cabinets. These monitors allow Argus displays to be viewed at the nurse stations regardless of patient selection switch settings at the discussion stations. The monitors are driven by scan converters via the video distribution amplifiers (see PR 6, B-7).

Tape Loops. A production problem was discovered in the 45-second delay loops supplied to the Coronary Care Unit. These delay loops are vital to the printout of computer initiated alarms. The length of the tapes varied from 30 sec., which was too short to show an alarm, to 62 sec., which was too long to show the alarm. The method used in splicing the tapes also caused breakage at the splice after 10 to 48 hours of usage. When these facts became clear, production and testing techniques for the tape loops were improved by the supplier.

IBM 360/50 Communications. An IBM 360/50 communications interface, data pump, and control unit were installed on the LINC-8, enabling the LINC-8 to communicate with the 360/50 located on the main campus via the BCL switching system (see PR 5, E-1).

ECG Communication. A phone line was installed between the CCU computer room and the Department of Medicine at Jewish Hospital so that the ECG's of ambulatory patients could be evaluated by computer (see B-7). The signal from the Holter-Avionics Recorder was conditioned by a Hewlett-Packard amplifier and transmitted over the phone line by a voltage controlled oscillator (VCO). A cable was also run from the CCU to the fifth floor of Barnard Hospital for the purpose of evaluating ECG's of clinical research patients (see B-5). These signals were transmitted by a VCO which was driven by the output of an RF telemetry receiver. In the computer room, rotary switch selection of the desired line allows use of a common discriminator to demodulate the signals.

B-13. Revision of AMBAGES

Personnel: M. D. McDonald, BCL

Support: RR 00396

AMBAGES (see PR 6, B-3), a complex of PC and LINC-8 interpretive programs written to aid the debugging of programs in the Broadcast system, in its first version slowed the running of ARGUS down by a factor of 75. With the experience gained in writing the first version it was believed that this factor could be considerably diminished by means of some quite extensive modifications. So the AMBAGES system was completely rewritten and a factor of 40-50 achieved.

B-14. Data Compression Techniques for Electrocardiographic Signals

Personnel: R. H. Greenfield, BCL

Support: RR 00396

Two methods of compression were examined. The first is a compression of data via the Aztec algorithm. This is done by removing the code bits used by Argus and recasting the Aztec output into a form using successive differences. The use of this algorithm results in a compression factor of 10 for electrocardiographic data sampled at 500 samples per second. The second method involves recasting the sampled ECG data into successive differences and approximating the resulting differences with powers of two. This method results in a compression factor of three.

B-15. Analysis of Slopes in the Electrocardiogram

Personnel: C. F. Pieper, BCL
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Support: RR 00396

Digital computer algorithms for detection of QRS complexes in the electrocardiogram commonly base their decision on the presence or absence of a QRS complex by comparing the first derivative with a threshold value. The Primitive processor in the Argus system detects the presence of a QRS complex ("forward R-wave" or "backward R-wave") using a relatively complicated contextual analysis of the sequence of Aztec slopes and bounds to differentiate QRS complexes from other non-QRS waveforms. In this manner, QRS complexes having a relatively slow depolarization sequence (often abnormal beats such as premature ventricular contractions) are retained while other waveforms producing a relatively sharp deflection (often the end slope of T waves, especially in combination with ST elevation or depression) are rejected. It was the purpose of this study to evaluate the performance of the Primitive processor by analyzing the magnitudes of the Aztec[1] slope analog of the first derivative $\delta(S) = \nu(S)/\tau(S)$, for all waves in the surface electrocardiogram.

From a previous evaluation of the Argus system (see B-1), widely varying clinical data from 34 patients were available consisting of time correlated Aztec[1], Primitive[2], and Cycle[3] data streams. Considering all slopes whose value $\nu(S)$ attained or exceeded the Primitive processor's criteria for a large grade g_L in quiet data, two digital plotter graphs were produced for each patient. The first graph marked the positions in the $\nu(S)$-$\tau(S)$ plane of the steepest slope (slope having the maximum $|\delta(S)|$) within each QRS complex identified by Argus. The second graph marked positions for slopes in waveforms labeled non-QRS by Argus. The reliability of the data was enhanced by spot checking the plotted points with the original waveforms, especially when the points fell in a region of relatively gradual slopes.

Preliminary evaluation of the results indicates that for the steepest slopes of QRS complexes the minimum $|\delta(S)|$ was approximately twice the minimum $|\delta(S)|$ of all Aztec slopes. Moreover, for T waves of normally conducted QRS complexes, the maximum $|\delta(S)|$ was also approximately twice the minimum $|\delta(S)|$ of all Aztec slopes. Occasionally, baseline shifts in segments where Argus failed to detect significant artifact, T waves of PVC's and large amplitude P waves had values for $|\delta(S)|$ in excess of twice the minimum $|\delta(S)|$ of all Aztec slopes. Thus, it is possible that some refinement of the Primitive algorithm may be made, especially for further differentiation of PVC's having very slow depolarization patterns from occasional very sharp and narrow T waves of normal QRS complexes. In other situations it is obvious that further improvements in Argus' performance may only be made by higher level contextual analysis.

(1) J. R. Cox, H. A. Fozzard, F. M. Nolle, and G. C. Oliver, Jr., "AZTEC, a Preprocessing Program for Real-Time ECG Rhythm Analysis," IEEE Transactions on Biomedical Engineering, Vol. BME-15, No. 2, pp 128-129, April, 1968.

(2) J. R. Cox, Jr., F. M. Nolle, G. C. Oliver, and H. A. Fozzard, "Some Data Transformations Useful in Electrocardiography," Computers in Biomedical Research, Vol. III, edited by Stacy and Waxman, Academic Press, 1969.

(3) F. M. Nolle and K. W. Clark, "Detection of Premature Ventricular Contractions Using an Algorithm for Cataloging QRS Complexes," Proceedings of the San Diego Biomedical Symposium (in press).

C-1. Workshop on Computer Processing of Dynamic Images from an Anger Scintillation Camera

Personnel: Staff Members from BCL, CSL, and Radiology

Support: RR 00396
Washington University

A workshop on computer processing of dynamic images from an Anger scintillation camera was organized and implemented with the objective of exploring the value of dynamic imaging as a clinical tool in nuclear medicine. The Workshop was held at the Washington University School of Medicine during the week of January 18-22, 1971.

The Workshop was intended to provide specialists in nuclear medicine, nuclear instrumentation, and digital computer engineering with information on aspects of camera-computer interface design for dynamic imaging by means of the Anger camera. Lectures and demonstrations were given by invited speakers and by members of the Washington University Computer Laboratories and the Department of Radiology of the Washington University School of Medicine.

During the first three days of the Workshop, information was presented on the physical principles and electronic design aspects of gamma-ray cameras and on logic and interface design fundamentals relating to the processing of dynamic image data from such devices. The design of the Washington University camera-computer interface was described in some detail, and examples of various computer programs using the interface were given.

The fourth day of the Workshop was dedicated to a pair of somewhat more theoretical topics - statistical and numerical analysis of dynamic tracer data and mathematical modeling, both compartmental and non-compartmental, of regional and organ blood flow.

In addition to being a presentation of the current state of the art with respect to technical problems in using the Anger camera, the Workshop was intended as a forum for critical discussion of the usefulness and the limitations of dynamic imaging of radionuclides as a clinical tool and as an instrument for research in physiology. To this end, the fifth and last day of the Workshop was devoted to presentations in which the potential clinical applications of dynamic imaging were evaluated and discussed by five panels of internationally recognized experts in nuclear medicine, radiology, and physiology. The topics discussed were: (1) models for interpretation of dynamic tracer data; (2) the use of the Anger scintillation camera interfaced to a computer for studies of regional cerebral function; (3) the use of the Anger scintillation camera interfaced to a computer for studies of the lung; (4) the use of the Anger scintillation camera interfaced to a computer for studies of the kidney; and (5) multi-tracer techniques and their probable influence on the future evolution of gamma ray cameras.

On completion of the Workshop, the notes which were provided the participants were revised, edited, and compiled to form the Workshop Proceedings which are being published in two volumes[1].

[1] K. B. Larson and J. R. Cox, Jr., editors, "Computer Processing of Dynamic Images from an Anger Scintillation Camera," Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971. In two volumes: Volume I. Design Considerations, Data Analysis, and Modeling; Volume II. Summaries of Panel Discussions.

C-2. Gamma Camera Interface to the PDP-12

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The interface design described in PR 6, C-6 has been implemented and tested[1,2]. The only additional feature to be added was that of presetting the number of counts to be collected within an array of data. This can be useful for collecting arrays of consistant statistical quality. Another feature that will be added allows the simultaneous dual-isotope feature of the new gamma camera to be used by the Nuclear Medicine Department to direct events to one of two arrays depending on energy. The interface is in operation and has been used to collect data for projects described in C-5, C-7, C-8 and C-9 of this report.

[1] R. L. Hill and J. R. Cox, Jr., "Detailed Design of the Washington University PDP-12 Interface", in: Computer Processing of Dynamic Images from an Anger Scintillation Camera, Vol. I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971.

[2] R. L. Hill and J. R. Cox, Jr., "A Gamma Camera Interface to a Small Computer," presented at the Symposium on the Sharing of Computer Programs and Technology in Nuclear Medicine, Oak Ridge, Tennessee, April 2-3, 1971.

C-3. A Data Collection Program for the PDP-12

Personnel: R. L. Hill, BCL

Support: RR 00396

A general purpose data collection program has been written[1,2] to collect 32x32 arrays of data from the gamma camera successively in time and store them in a specific format on LINC tape. The accummulation time for each array is a variable specified by the user and can be a minimum of 3/8 second or possibly 1/8 second if data compression techniques are employed. Data collection and tape operations use separate direct memory access channels and can occur simultaneously, leaving the processor of the PDP-12 free to do data compression of previously collected data or to clear an area in core memory for collection of a future frame. A study can thus be performed without any data loss.

Studies of up to 120 frames can be stored on a single tape, and a filing system allows multiple short studies to be stored on the same tape. Provision is made in the programs for collecting a background array and an array of data from a flood of the camera to allow for subsequent correction of data for the nonuniform spatial response of the gamma camera. Alphanumeric data pertaining to the patient can be entered and stored on tape with each study.

(1) R. L. Hill, "Data Collection with the PDP-12," in: Computer Processing of Dynamic Images from an Anger Scintillation Camera, Vol. I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971.

(2) R. L. Hill. and J. R. Cox, Jr., " A System of Programs for a Small Computer Interfaced to a Gamma Camera," presented at the Symposium on the Sharing of Computer Programs and Technology in Nuclear Medicine, Oak Ridge, Tennessee, April 2-3, 1971.

C-4. Analysis of Dead Time Effects

Personnel: R. L. Hill, BCL
J. R. Cox, Jr., BCL

Support: RR 00396

The gamma camera interfaced to a small computer can be modeled as a succession of devices, each requiring a finite time to process a nuclear event. When a nuclear event occurs during this "dead time" one of the devices is busy with a previous event and the new event is lost. For dynamic studies, it is necessary to reconstruct accurately the true count rate of the process generating events. A technique for correcting the received count rate for lost events has been established(1), but for the camera-computer system this has limited application since it is valid only for a single, non-paralyzable dead-time system.

In order to assess the validity of the correction technique, a program was written for the IBM 360/50 to simulate the camera-computer system with a Poisson-process of known rate as input to the system. Received count rates were corrected for a 15 μsec dead time, that of the analog-to-digital converters, the longest in the system. Error between corrected count rate and known true rate were calculated for increasing count rates using as a parameter the probability that an event was accepted by the pulse height analyzer of the gamma camera. Results(2) indicate that for total counting rates above 40 to 50 thousand counts per second, error from the correction becomes intolerable, above 5%. Reducing the dead time of the analog-to-digital converters to 5 μsec, that of the gamma camera, does not greatly improve the situation; therefore, more expensive converters are not clearly indicated.

(1) R. D. Evans, "The Atomic Nucleus", Chapter 28, McGraw-Hill, 1955.

(2) J. R. Cox, Jr., and R. L. Hill, "Interface Design Considerations," in: Computer Processing of Dynamic Images from an Anger Scintillation Camera, Vol. I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971.

C-5. Ventilation-Perfusion Studies Using the Gamma Camera

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A system has been designed to measure regional ventilation using ^{133}Xe and a Pho-gamma III scintillation camera interfaced to a PDP-12 computer (see C-2). The ^{133}Xe is administered from a specially constructed closed system consisting of a 236 liter bag box containing two ballons, a wedge spirometer and the necessary connecting tubes, valves and mouthpiece.

Single breath studies, and washin and washout studies have been carried out on 50 subjects - 11 normal individuals and 39 patients. Each of the patients has also had a perfusion lung scan using Indium 113^m ferric hydroxide particles. The data from each study is stored on magnetic tape (see C-3) and consists of a uniformity array, background counts, a single breath frame and then sequential images of the washin and washout of ^{133}Xe. The images of the perfusion scan are stored on a separate magnetic tape. Programs have been written to view sequential images, and counts in selected regions of each lung, so that the fractional exchange of air per breath can be determined for such regions. In addition activity-time plots can be displayed.

A correction for the overlying tissue content of ^{133}Xe has been devised, using an area beneath the lung images as representative of the changes in tissue ^{133}Xe concentration. In spite of theoretical objections, observations in a patient with a pneumonectomy suggest that this may be a practical way of overcoming this problem.

Patients with defects in perfusion due to chronic obstructive lung disease were readily distinguished from those due to pulmonary embolism by the ventilation studies. In addition the mean values for the percent of air exchanged per breath are significantly lower in patients with chronic obstructive lung disease than in either the normal individuals or in the patients with pulmonary embolism.

A data preprocessing program to correct for non-uniformity, background activity, dead time loss and isotope decay, and a special calculation program for this data are nearing completion.

We propose now to compare the washout from a single breath and also from an intravenous injection of ^{133}Xe, with the figures derived from the washin and washout studies. These methods will then be compared to transmission radiography (see PR 5, D-5).

C-6. Regional Lung Water

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Preliminary experiments using the gamma camera interface to the PC computer have been carried out to examine the feasibility of measuring regional lung water. Localized pulmonary edema was produced in mongrel dogs by the intrabronchial injection of 10-15 mls of Hypaque into the right lower lobe bronchus. Chest radiographs show the rapid appearance of edema which clears within 24 hours. After production of localized edema the mongrel dogs were given sequential injections of ^{15}O-labelled water and ^{113m}In-labelled transferrin (as an intravascular marker) or ^{131}I-antipyrene (as a water indicator) and ^{113m}In-transferrin. Perfusion lung scans using ^{113m}In-ferric hydroxcide particles were also carried out to demonstrate pulmonary arterial blood flow. The experiments showed that there was reduced blood flow and blood volume in the edematous region and that the water content of this region was greater than in the contralateral lung. Observations on the activity-time curves from these regions, selected through the PC, showed differences in the shapes of the transit curves for the isotopes but the count rate was too low for reasonable statistics. A multiple probe system, with at least two pulse height analyzers per probe, is being assembled so that the first passage of two simultaneously injected isotopes can be recorded. The difference in mean transit time of the intravascular and water indicators is directly proportional to the difference in their volumes of distribution and hence will give a measure of extravascular lung water.

C-7. Cardiac Ejection Fraction

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The cardiac ejection fraction, or the percentage difference between the contents of the left ventricle at the end of diastole and the end of systole is probably one of the most sensitive indices of cardiac function. A non-invasive method of measuring this has been described in which radionuclide images of the cardiac blood pool at end-systole and end diastole were recorded on 35 mm film(1). The R-wave of the electrocardiogram was used to trigger the gamma camera pictures. Subsequent analysis was by graphic and planimetric methods on projected images of these pictures.

We are implementing a similar technique using the Pho-Gamma III camera interfaced to the PDP-12. The study is performed following the bolus injection of ^{99m}Tc-labelled human serum albumin. Sequential 0.5 second frames are collected during the passage of the radionuclide through the heart followed by integrated pictures of an end-systolic and an end-diastolic image. The position of the base of the left ventricle is determined from the bolus injection and the changes in size, shape and content of the left ventricle from the two integrated pictures. For the end-diastolic picture four consecutive 15 msec frames are continuously collected but stored temporarily in a circular buffer and only transferred to a second buffer when the R-wave occurs. The end-systolic picture is collected for the last 40 msec of the T-wave and assumes a constant R-T interval in any individual. The position of the end of the T-wave to be selected is set up using cursors at the time of the study.

Preliminary experiments have been performed to determine the best view for this procedure and integrated images of both end-systole and end-diastole have also been collected using sodium pertechnetate-^{99m}Tc, demonstrating the feasibility of this method.

(1) B. L. Zaret, H. W. Strauss, and P. J. Hurley et. al. "Left Ventricular Ejection Fraction and Regional Myocardial Peformance in Man Without Cardiac Catheterization." Circulation, 212: Suppl. 3., 120, 1970.

C-8. Computer Assisted Renography

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Support: RR 00396
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Work carried out elsewhere using external probes suggested that subtraction of the tissue and blood background components from a conventional renogram yielded tracings of a more physiological nature, from which the relative effective renal plasma flow, relative outflow of ^{131}I-Hippuran and the transport efficiency of each kidney could be determined.

For studies with the gamma camera, the Pho-Gamma III interfaced to the PDP-12 is used. Scintiphotos of the kidneys using ^{197}Hg-chlomerodrin are obtained for localization, and then stored on the data tape so that each kidney can be clearly outlined for the Renogram. Following injection of

^{133}I-Hippuran data is collected at 20 second intervals for twenty minutes. Activity-time curves are then generated from the regions of interest and a third tracing can be generated from the region caudad to the kidneys for the tissue correction. Relative effective renal plasma flow is readily determined from the relative areas beneath the kidney traces before the first peak is reached - that is before any ^{131}I-Hippuran has left the kidneys.

Further work envisages the use of ^{123}I-Hippuran to improve the count rate, an external probe connected through the same interface to indicate overall renal clearance and a dual isotope technique for depth detection.

C-9. Gastric Emptying Study

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The rates of emptying of various solutions and meals by the stomach have been studied *in vivo* using orally administered radioactive tracers and the data collection and processing facilities of a PDP-12 computer interfaced to a gamma camera (see C-2). After sequential frames of 32 x 32 digitized data have been collected by the computer and stored on magnetic tape, (see C-3), the data frames are integrated over time and the area of the stomach is outlined by the user as the image of the integrated data is generated on the display screen of the PDP-12 (see C-13). Then linear, semilog and square root regression analyses of the concentration of activity in the stomach as a function of time are performed on the PDP-12.

The method has been used to date to evaluate gastric emptying in patients with hypoglycemic disorders. No significant differences have been found between these patients and normal controls. Future studies are planned to evaluate the effects of drugs and surgical procedures on gastric physiology.

C-10. A Computer Based Calibration System for a Gamma Camera

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Support: RR 00396

Some of the physical properties of the gamma camera that should be investigated for each system are:

(a) Energy resolution

(b) Dead time

(c) Spatial resolution

(d) Spatial distortion

(e) Nonuniformity of response over the camera face

A computer based calibration system has been developed to assist in the investigation of these physical properties[(1)]. Five different gamma ray emmiting sources ranging from 50 kev to 550 kev were used to evaluate the energy resolution of the gamma camera. Special capillary tubing filled with these sources provided the line sources for spatial resolution and distortion studies. Hollow plexiglass discs filled with these sources provided uniform flood sources for nonuniformity studies.

In addition to the sources and techniques suggested to study the gamma camera, a complete software system has been developed for the DEC PDP-12 computer interfaced to a gamma camera to collect, store, and analyze the data. The programs reside on a LINC tape and may be requested by a user's command. These consist of a data filing program, a data collection program, display programs, a spatial resolution program using a modulation transfer function technique, a spatial distortion program, and dead time and printout programs.

This system has been designed for a 64x64 array and may be used in clinical research for static studies.

(1) N. A. Mullani and S. C. Huang, "Gamma Camera Calibration Procedures and Programs," in: Computer Processing of Dynamic Images from an Anger Scintillation Camera, Vol. I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971.

C-11. Retrieval of Gamma Camera Data via 35mm Photographic Film

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A system for gathering gamma camera data via 35mm photographic film and for retrieving the data with a flying spot densitometer under control of the University's IBM 360/50 was described in PR 6, C-7. This system has been evaluated by comparing its ability to detect regional scintillation concentration with the ability of an on-line, digital computer interfaced to the gamma camera through analog-to-digital converters. The comparison has required the design and construction of a electronic fiducial marking device that outlines on the film the area viewed by the computer's analog-to-digital conversion system. For a narrow range of regional data concentration, the 35mm film system and the on-line digital-computer system are equally effective. The 35mm film system lacks the information capacity of the on-line digital-computer system. To facilitate dynamic tracer studies with the 35mm film system, a low-cost paper-tape camera controller has been built that provides contiguous data collection intervals of variable duration.

C-12. OPERAS

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Support: RR 00396

OPERAS (OPERAtor System)(1) was designed because of a need for the ability to perform extensive calculation with speed and accuracy on large amounts of empirical data collected by means of the Anger scintillation camera. It was written for an 8K DEC PDP-12 computer and occupies 3000_8 words of core.

The system is utilized by being presented with commands in the form of coded operand, operator pairs. The operator defines a function to be performed on the explicitly designated operand and one or more implicit operands. Operands fall into one of two classes, scalars (single members) and arrays (sets of 1024 numbers).

Double-precision binary floating-point routines were written for handling scalar variables while a block floating-point scheme were developed for arrays.

(1) M. D. McDonald and C. S. Coble, "Operator System", in: Computer Processing of Dynamic Images from an Anger Scintillation Camera, Vol. I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971.

C-13. Display Routines for the PDP-12

Personnel: J. M. Baker, BCL

Support: RR 00396

Display routines[1] have been written for the PDP-12 computer with cathode-ray tube output to provide visual presentation of radioisotope distributions as detected by a gamma camera. The displays include shades-of-grey images of the spatial distribution of isotope and rectilinear plots of the regional count rate as a function of time. These displays have a variety of controllable parameters and interactive features. The interactive features enable the user to specify what spatial and temporal portions of the data to use in subsequent analysis.

A utility program has been written for the PDP-12 to assist in the analysis of dynamic tracer study data. This program uses the shades-of-grey displays and the rectilinear plot for ciné play-back of the tracer study, selection of a region of interest, and plotting of the count rate as a function of time for a selected region.

Another utility program has been written for the PDP-12 to provide a variety of transformations applicable to the regional count rate functions. These transformations include function inversion, scaling, smoothing, subtracting of functions, and others. This program also plots the functions and transformed functions, one or many simultaneously.

(1) J. M. Baker, "Display Programs for the PDP-12", in: Computer Processing of Dynamic Images from an Anger Scintillation Camera, Vol. I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971.

C-14. Compartmental Modeling

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Support: RR 00396

Our approach to the development of compartmental modeling techniques was described generally in PR 6, F-13. As part of our effort to understand the limitations of compartmental analysis, we have continued to study the condition of the exponential fitting problem[1]. We are applying compartmental analysis techniques to the study of several systems (see C-15, C-16 and F-2).

Our search for alternatives or extensions to compartmental analysis for the extraction of the information available in kinetic radioisotope data has led us to an analysis of a general clearance curve[2]. The general principles for deciding that a given curve should be called a sum of n exponential terms are: (a) if the best fit with n-1 terms is not a "good" fit, as evidenced by systematic deviations between the observed and predicted curves, and (b) if the best fit with n+1 terms is too "poorly conditioned," as evidenced by very large standard deviations associated with the best fit parameters, and (c) if the fit with n terms is "good" and "well-conditioned." These criteria are highly subjective and it is sometimes difficult to decide whether a given curve should be considered a sum of three or four (say) exponential terms. Therefore, we have been seeking more "robust" measures of the information available in a curve, such as its moments, in terms of the compartmental parameters. This work is promising and is being prepared for publication. We are also seeking to get these "robust" measures with integral transform techniques.

We have extracted the exponential fitting technique used in Berman's Simulation, Analysis and Modeling (SAAM) program (see PR 6, C-10) and have tested our version with annew IBM 360/50 Fortran program and plan to implement it on the PDP-12.

(1) M. L. Rockoff and J. Markham, "Fitting Data with Linear Combinations of Exponentials", in: Computer Processing of Dynamic Images from an Anger Scintillation Camera, Vol. I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971.

(2) M. L. Rockoff, "Notes on the Interpretation of a Clearance Curve in Terms of Compartmental Analysis", in: Computer Processing of Dynamic Images from an Anger Scintillation Camera, Vol. I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971.

C-15. Compartmental Model of Myocardial Blood Flow

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Myocardial blood flow is being studied by external monitoring of the radioactive tracers, oxygen-15 labeled water and xenon-133. Both are diffusible tracers, but for the latter recirculation cannot be ignored and the usual clearance curve analysis (see C-14) does not seem to be applicable. Therefore, we are seeking a compartmental model which will take recirculation into account.

C-16. Kidney Experiments Using Short Lived Isotopes

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Oxygen 15 in the form of oxygen-15 labeled water, oxygen-15 labeled hemoglobin and oxygen-15 labeled carboxyhemoglobin has been utilized in determination of the renal blood flow, the renal oxygen consumption, and the renal vascular volume in experimental animals. The isotopes were produced by the cyclotron of the Washington University School of Medicine.

In this experiment a Linc was used for data acquisition and storage, decay and background correction, and for data transfer to the IBM 360/50 on main campus for analysis. The Linc probe system has been described in more detail in the proceedings of the Gamma Camera Workshop[1]. A description of the experiment has been prepared for publication[2].

Recently an additional scintillation probe was installed in the abdominal special procedures room on the third floor of the Mallinckrodt Institute of Radiology. This probe is connected via a 200 foot cable to the Linc allowing us to perform renal blood flow studies in patients at the time of angiography.

The washout curves obtained from either animal or human flow studies were analyzed in three ways:

1. Manual analysis consisting of conventional curve stripping and determination of mean flow by the initial-slope method.

2. Mean flow calculations according to Zierler's H/A method using the Linc.

3. Computer analysis by fitting the data with linear combinations of exponentials using SAAM on the IBM 360/50 (see C-14).

The results of the different types of analysis are being compared. In addition, studies of the renal blood flow were performed in the same dog using Xenon-133 as a diffusible indicator. The washout curves of these experiments are being subjected to the same analysis and are being compared with the data from the oxygen-15 labeled water experiments.

(1) C. Coble, N. Mullani, J. Eichling, and P. Peters, "LINC-Probe System," in: Computer Processing of Dynamic Images from an Anger Scintillation Camera, Vol. I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971.

(2) P. E. Peters, M. M. Ter-Pogossian, M. L. Rockoff, J. M. Metzger, and P. R. Koehler, "Measurement of Renal Blood Flow by Means of Radioactive Water Labeled with Oxygen-15," submitted for publication.

C-17. External Monitoring of Radiotracers in the Presence of Recirculation

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The interpretation of kinetic tracer data obtained by external monitoring of radioactive-labelled indicators is generally based on mathematical models that ignore recirculation. An important limitation of these models is that they can be used successfully only in those situations in which the major portion of the response curves are obtainable prior to the onset of the first recirculation. A further complication that limits the usefulness of the models is due to interference from radiotracer carried by recirculation into perfused regions adjacent to the organ or region of interest and in the field of view of the detectors.

We have developed a mathematical model applicable for external monitoring when recirculation is not a late event and must be taken into consideration. Also, the model accounts for interferring perfused regions in the field of view of the detector. Central to the model is the use of two injections of tracer, one upstream (arterial) one downstream (venous) of the particular organ of interest; thus, two residue curves are obtained. We have developed equations indicating how to process the two residue curves in order to determine the mean transit time of tracer through the organ of interest, as well as higher moments if they are desired. These equations are natural generalizations of Zierler's "H/A" method(1) in that they are transport-model free. The numerical calculations do not rely on curve fitting. We can also determine compartmental parameters if these are appropriate and desired. A description of the method is being prepared for publication(2).

Computer programs to implement our equations are being written for both the Washington University IBM 360/50 and the LINC. Experimental results which have been obtained by one of us (J.O.E.) for the cerebral circulations of anesthetized dogs using arterial and venous injections of ^{133}Xe and of ^{15}O-labelled water will be used to test the method with actual data.

(1) K. L. Zierler, "Equations for Measuring Blood Flow by External Monitoring of Radioisotopes," Circ. Res., 16: 309; 1965.

(2) K. B. Larson, D. L. Snyder, J. O. Eichling, "Measurement of Blood Flow by External Monitoring of Radiotracers with Interference Due to Recirculation and Perfusion of Adjacent Tissues," to be submitted for publication.

C-18. The Interpretation of Data from Tracer Kinetic Experiments

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By solving the general convective diffusion equation for transport of tracer in a vascular system consisting of vascular fluid and an arbitrary number of tissue phases, we have shown in a rigorous fashion that the mean transit time $\bar{t}$ of traced substance through the system is independent of non-convective transport parameters such as indicator diffusivities in tissue and in blood and capillary permeabilities, provided that $\bar{t}$ is measured by residue detection. The same result is obtained for outflow detection only when there is no diffusion of traced substance across the system boundaries, i.e., when the sole mechanism of tracer transport into and out of the system is convection. For both of these cases, the "central volume principle" of indicator dilution theory[1,2] holds exactly for the non-steady-state, even though involving equilibrium partition coefficients. This somewhat counterintuitive result is contrary to the widely-held belief that, in the dynamic situation, the appropriate partition coefficients are time-average concentration ratios rather than equilibrium values.

We have confirmed the above general result for four special models of flow in a vascular system representing the extremes of physically realizable mass transport. The four cases are: 1) complete dispersion in the blood phase with diffusive equilibrium in the tissue phases (the "compartmental" assumption); 2) no dispersion in the blood phase with diffusive equilibrium in the tissue phases; 3) complete dispersion in the blood phase with lack of diffusive equilibrium in the tissue phases; and 4) no dispersion in the blood phase with lack of diffusive equilibrium in the tissue phases. In all four of these special cases we found, as in the general case, that the mean transit time of traced substance through the system was independent of the diffusion coefficients in the tissue phases.

While the mean transit time is independent of the details of diffusive transport, higher moments of the transit-time distribution are model-dependent and will in general involve transport parameters. The results summarized here are being prepared for publication[3].

(1) K. L. Zierler, "Equations for Measuring Blood Flow by External Monitoring of Radioisotopes," Circ. Res. 16, 309, 1965.

(2) J. L. Stephenson, "Theory of Measurement of Blood Flow by Dye Dilution Technique," IRE Trans. Med. Electronics PGME-12; 82, 1958.

(3) G. W. Roberts, K. B. Larson, and E. E. Spaeth, "The Interpretation of Data From Tracer Kinetic Experiments," to be submitted for publication.

C-19. Parameter Estimation of Radioisotope-Tracer Data

Personnel: D. L. Snyder, BCL

Support: RR 00396

The objective of this continuing study (see PR 6, C-13), is to develop efficient computer techniques for processing radioisotope tracer data from gamma camera and probe array detectors under low count-rate conditions when histograms are so noisy that more conventional curve-fitting procedures do not work well. The procedure is based on the collection of arrival times or, equivalently, interarrival times associated with the detection of individual gamma-photons. While more difficult to collect and process, these arrival times contain more information about the transport of tracer than histograms.

An interface to the LINC computer has been designed and constructed for the collection on LINC-tape of the interarrival times of gamma-photons in a single scintillation detector (see C-21).

The approach we have taken is to describe the time evolution of the posterior statistics of parameters of the count-rate function in terms of the collected arrival or interarrival times. Estimates of the parameters can in principle be determined from these posterior statistics; but, in practice, the equations are too complicated for exact realization on a computer, especially a small one. For this reason, we have developed certain approximate estimates that are quite feasible for machine implementation(1). We have examined the accuracy of these approximations by comparing the approximate and exact estimates in several simulation studies. The results(1) indicate a close agreement even under very low count-rate conditions.

Some preliminary experiments with real data were conducted. In these, interarrival times were collected for gamma-photon emissions in the natural decay of oxygen-15 in labeled water. These times were processed in order to estimate the mean life of oxygen-15. The results(2) were in very good agreement with published values for the mean life even though the initial count rate was low (about 600 c/s) and only about 400 seconds of data were collected.

(1) D. L. Snyder, "Approximate Filtering for a Poisson Process with a Stochastic Intensity Function," BCL Monograph No. 140; July, 1970.

(2) D. L. Snyder, "Statistical Analysis of Radioisitope Tracer Data," in: Computer Processing of Dynamic Images from an Anger Scintillation Camera, Vol. I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971.

C-20. Reducing the Motion Artifact in Clinical Scintillation Images

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Support: RR 00396

An algorithm(1) for reducing respiratory motion artifact in scintillation scans using only the external monitoring capabilities of the gamma camera has been implemented and evaluated. Simulated clinical data is collected in 64 x 64 digitized arrays via a PDP-12 computer interfaced to a gamma camera (see C-3). After the collected data has been transferred to 7-track magnetic tape, it is processed by the University's IBM 360/50 computer and returned to the PDP-12 for display using programs described in C-13. The images derived from identical data, with and without the application of the artifact correction, have been compared, verifying the clinical significance of the computational procedure(1).

(1) B. E. Oppenheim, "A Method for Reducing Respiratory Artifact on Liver Scans Made with a Camera, Using a Digital Computer," to be published in Journal of Nuclear Medicine.

C-21. Event Interarrival Time Measurements

Personnel: N. A. Mullani, BCL
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Support: RR 00396

An interface has been designed and built for the classic LINC to measure the interarrival time of events. This interface consists of a twenty-two bit presettable clock which can be used either as a real-time clock or to measure interarrival times. In the real time mode of operation the contents of the clock register can be transferred to memory under program control or a flag can be set on overflow of the clock. In the interarrival time mode the LINC is in a paused condition between arrivals of events. When an event is registered at the interface, the interface will record the last interarrival time by transferring the contents of the clock register to the memory and will increment by one the memory address. The interface will transfer either eleven bits or twenty-two bits depending on the time duration between the last two events. When the memory address reaches 4000_8, the interface releases the LINC from the paused state and puts it back in normal running condition under program control.

The clock is driven by the LINC crystal clock at either the basic 500 kHz rate, or at 250 kHz, 125 kHz, or 62.5 kHz. The starting location of data transfer to the memory is loaded into the accumulator before the program engages the interface. The clock can be turned on or off under program control.

This interface is primarily used to measure the time between arrivals of events that are thought to be Poisson. The intensity of the Poisson process is estimated from the interarrival times by an iterative process (see C-19).

C-22. Evaluation of Oxygen-15 Half Life

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Support: RR 00396
GM 14889

Estimates of the half life of oxygen-15 are reported in the literature ranging from 122 to 126 seconds. In clinical research utilizing ^{15}O the duration of the experiment may extend for ten half lives. The percentage error in the decay correction of the data is given approximately by

$$\left[1 - \left(e^{\lambda t}\right)^{\frac{-\Delta t}{\tau}}\right] X\ 100$$

where λ is the decay constant

t is the elapsed time

τ is the half life

and Δt is the error in the half life. Within the range of the reported values for the half life of ^{15}O this can result in a percentage error as large as 11% over ten half lives and for an error $\Delta t=2$ seconds.

Samples of pure ^{15}O are produced by the $^{14}N(d,n)^{15}O$ reaction at the cyclotron at the Washington University School of Medicine. The decay of ^{15}O is followed using a NaI detector interfaced to a LINC computer. The data is then analyzed on an IBM 360/50 computer by a least squares technique. In addition, interarrival times are collected and processed according to the procedure described in C-19.

This study will also be extended to include half life determination for ^{13}N and ^{11}C.

C-23. Design of the Multiprobe System for Tracer Kinetics Studies

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A multiple probe system consisting of twenty-six 2" x 2" NaI(Tl) detectors with focusing collimators is being designed and constructed. This system will replace the six probe system that is presently used for human cerebral studies. The twenty-six probe system will provide an improvement in spatial resolution and data acquisition rate as compared to the six probe system. The multiple probe system will be interfaced to a small digital computer for data acquisition, storage, and analysis. Design considerations for a fast and completely parallel interface are underway. We are also considering the possibility of an automatic calibration system for normalizing the output of each probe.

C-24. Oxygen, Glucose Metabolism Studies

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An investigation of the behavior and fate of ^{11}C-labeled glucose and ^{15}O-labeled oxygen are being carried out in an attempt to determine whether these labeled metabolites might be useful in (1) identifying brain tumors and (2) localizing brain tumors. It appears that a certain portion of the injected glucose is metabolized in the brain, and it is possible that brain tumors might metabolize glucose at a rate different from normal cerebral structures. Furthermore, it is quite conceivable that different types of brain tumors would metabolize glucose at different rates, and also, that this rate may be different for other types of cerebral pathology (such as infarcts). This possibility is supported by our previous studies indicating that some glioblastomas utilize more oxygen (via ^{15}O) than normal cerebral tissues and presumably they would also utilize more glucose. It should be noted that all the agents presently used for localization of brain tumors by scintiscanning (pertechnetate, albumin, chloromedrin, etc.)

rely for the concentration in neoplastic tissues on a break of the blood brain barrier, thus they are injury specific rather than tumor specific, while glucose might supply us with a tumor specific agent since it is a metabolite.

The oxygen-glucose studies also include the study of the effect of ethanol, marijuana, and other psychoactive drugs on cerebral metabolism.

The data from the six probe system is collected on the LINC with the aid of the six probe interface and the software already developed (see PR 6, C-9). Modifications were made to the collection program and new plot programs were written for efficient display of this specialized data.

C-25. A Software System for Radio-Gas-Liquid Chromatograph

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Support: RR 00396
GM 14889
HE 13851

A software system for radio-gas-liquid chromatograph system is being developed to assist in data acquisition, storage, and analysis (see PR 6, C-12).

The system runs under LAP 6 control and uses the free meta commands to load different programs. The programs available so far are:

a) Mass and radiation data collection

b) Load and store data

c) Data printout

d) Data display, correction and calculation

The data collection routines display the data as they are being collected and transforms the data into single or double precision words depending on the absolute value of the datum. A maximum of 1536 data points may be collected for integration times ranging from 0.125 secs. to 125 secs. per point.

The data are then stored in eight consecutive blocks on a data tape and filed in an index structure compatible with LAP 6. The display listing and editing of the data file are done with LAP 6.

Analysis of the data is done by an interactive method. The user determines the data display scaling factors, isotope used, flow rates, column temperature, and by means of a cursor, the beginning, ending, and height of an activity peak. The data are then corrected for decay, background, flow rate and temperature variations, and detector efficiency. The area under the peaks, retention times, peak maxima, percent of total activity for each peak, and total area for the entire experiment are then printed on the teletype.

C-26. Measurements on Blood Vessel Lengths Between Bifurcation Points

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Support: RR 00396
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The purpose of the measurement is to obtain length distributions of blood vessels between bifurcations. This information is required in a transit time model presently under development.

Length measurements are made from photomicrographs of blood vessels of rat skeletal muscle prepared in dry slides. Graphical data describing the arrangement of blood vessels are first recorded using the PC, a rho-theta device and the DRAW program (see PR 6, E-4). The graph data are then sent to the IBM 360/50 through the PC-360 communication system, and are processed to calculate blood vessel length. Finally, these length data are sent back to a LINC and stored on LINC tapes for interactive processing.

A LINC program was written whose main functions are: (1) regrouping data; (2) obtaining and displaying length distributions; and (3) displaying scatter diagrams. After interactive processing with this LINC program, data are again sent to the IBM 360/50 for various statistical analyses.

At present, the blood vessels measured are limited to those with diameters below 20μ. The preliminary results show that: (1) either exponential, gamma, or log-normal distributions can fit the length data within statistical tolerance; (2) it is consistent to assume for our data that lengths of adjacent blood vessels are statistically independent, but the mean length gets smaller (about 10%) after every bifurcation; (3) it is consistent to assume for our data that lengths of two blood vessels branching from a parent vessel are statistically independent.

C-27. Preliminary Experiments on Washout Studies of the Whole Heart

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Support: RR 00396
HE 13415
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These efforts were directed toward the eventual determination of the washout kinetics of calcium ion from whole heart *in vivo* using the gamma camera PDP-12 system. The objective is to measure the calcium ion washout from the cells themselves rather than from the extracellular space or vessels. This then enables the cellular calcium ion uptake to be obtained. It may also be possible to measure the uptake directly.

In the summer of 1970, several dog experiments were done in which the chest was opened, the left coronary artery was exposed on the beating heart, a catheter was inserted through an aortic puncture, curved around and pushed into the left coronary and confirmed by feeling the left coronary with a finger. There seemed to be a problem of maintaining the catheter in position long enough for transport and injection.

The data collection is to be synchronized with the ECG such that gamma events will be recorded near the peak diastole at maximum volume and the area presented will always be at the same part of the cardiac cycle so as not to "smear the picture." To this end an analog differentiator is employed to obtain the derivative of the ECG eliminating the base line variation with the respiratory cycle. The PC was programmed to sample this differentiated ECG, and display it while simultaneously displaying a horizontal line controlled by an analog knob for the purpose of setting a threshold for synchronization. This program was successful using the ECG from a dog.

Programming was also done for a predicted but speculative washout characteristic on the PC for the entire data collection. All of these programs are in the process of being revised and rewritten for the PDP-12.

One catheter experiment was done on a 60 lb. pig and it seems likely that the pig heart coronary geometry will be much better for inserting and maintaining catheter position in the left coronary artery from the femoral artery by use of a fluoroscope.

Equipment has been obtained for preliminary washout experiments on closed chest pigs using a three inch diameter gamma probe over the chest. a dual ratemeter and a two channel recorder. Calcium-47 will be used along with a suitable isotope which remains in the extracellular space, and differential dual-isotope washout experiments are planned. Some calcium-47 is in the process of being made at the Washington University Cyclotron Laboratory.

C-28. Differential Linearity of Analog-to-Digital Converters

Personnel: R. L. Hill, BCL
J. R. Cox, Jr., BCL
V. W. Gerth, Jr., BCL

Support: RR 00396

In order to assess analog-to-digital converters (ADC's) for the gamma camera interface application, differential linearity for two types of ADC's was measured. Differential linearity specifies the variability in bin size for an ADC. The average bin size for an n-bit converter is the full scale voltage range of the ADC divided by 2^n. This is of particular importance in this application since poor differential linearity could distort data collected from the gamma camera. For a successive approximations ADC, differential linearity is poor if all output bits are used. By using the seven most significant bits of a 12-bit ADC, we were able to show[1] a differential linearity of 1-2%. Using the seven least significant bits gave ±30-40% differential linearity. For the ramp converter which was actually used in the interface, differential linearity was measured at about ±5%. From this we can conclude that the usually less expensive successive approximation ADC, when used correctly is adequate for this application.

(1) J. R. Cox, Jr. and R. L. Hill, "Interface Design Considerations," in: Computer Processing of Dynamic Images from an Anger Scintillation Camera, Vol. I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, 1971.

D-1. Design of a Surgical Intensive Care Unit - General Considerations

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K. F. Bemberg, Barnes Hospital
G. J. Blaine, BCL
A. L. Bodicky, BCL
R. E. Clark, M.D., Surgery
V. W. Gerth, Jr., BCL
R. W. Hagen, BCL
J. M. Pexa, BCL
L. J. Thomas, M.D., BCL and Anesthesiology
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The design of a surgical intensive care unit (SICU) for patients undergoing cardiothoracic surgery was begun a little over a year ago. The collaboration between the Department of Surgery, Barnes Hospital and BCL has continued throughout the year with the design goals stated last year (see PR 6, D-2) met by the proposed design. Major equipment has been evaluated and ordered. The remaining work has been subdivided and reports follow on a video system for computer output, a digital communication system, the computer itself, analysis of transducers and signal conditioners, and architectural and mechanical considerations.

D-2. A Computer-Driven Video Display System for Surgical Intensive Care

Personnel: V. W. Gerth, Jr., BCL
J. R. Cox, Jr., BCL
R. W. Hagen, BCL

Support: RR 00396
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A Computer Driven Video Display System has been designed which provides capability for the display of both graphic and alphanumeric information while utilizing the economies of commercially available closed-circuit television hardware and ease of signal distribution. The system contains an adequate amount of internal storage so that the demands on computer memory cycles required to maintain the display are minimized. Since in the SICU, nine displays, each containing two channels of graphic information and one channel of alphanumeric information must be maintained simultaneously by a single computer, the storage internal to the display system is an essential feature.

A useful by-product of the internal storage is the availability of delayed graphic data, which may be used at the computer's option following detection of events of interest to produce hard copy. The system contains four major components: graphic generator, alphanumeric generator, timing generator, and video distribution. From the standpoint of the computer, the timing and video distribution sections are unseen and only the graphic and alphanumeric generators are of concern.

Graphics and alphanumerics are independent until their final video signals are merged into one video stream which is distributed to monitors throughout the SICU. The alphanumeric generator accepts codes from the computer and then refreshes indefinitely with no scheduled updating necessary. Single character random updating is then possible at the convenience of the computer. The capability of the alphanumeric generator to refresh automatically, relieves the computer of a significant burden especially when the information is essentially static as in the case of labelling of graphic axes.

The graphic generator normally operates in the "scroll" mode in which the waveform moves across the screen from right to left with the newest information appearing at the right and the oldest disappearing at the left. This creates the effect of a chart recording being moved past a 4 second window. The trace has uniform intensity across the screen and allows close scrutiny of an event of interest as it progresses from right to left. If desired, the scroll display can be shifted to the "static" mode where the waveform is continuously refreshed and does not move across the screen.

The timing generator is the source of the composite sync waveform required by standard CCTV monitors and, in addition, provides timing signals to both the alphanumeric and graphic generators. Clock signals to drive the storage shift registers, and an 18-bit address which corresponds to the position of the beam within the TV raster at any time are also provided by the timing generator. Nine bits of the address are interpreted as a scan line number and the other nine bits represent the displacement along a given scan line. The video distribution section adapts the digital video and composite sync signals for transmission on coaxial cables.

At present, various elements of the system are being breadboarded to provide a basis for selection of final components.

D-3. A Communication System for Surgical Intensive Care

Personnel: G. J. Blaine, BCL
J. R. Cox, Jr., BCL
J. M. Pexa, BCL

Support: RR 00396
Washington University

The SICU Monitoring System requires both data acquisition and data distribution. A data communication system has been designed to address both requirements.

The data acquisition requirement consists of the means for the delivery to the computer of sampled values of physiological variables. Data distribution involves delivery of computed results to the bedside, to the physicians discussion station, and to the central nurses station. In addition, communication paths must be provided to allow data entry from special equipment (i.e., blood gas analyzer) to the computer, intercomputer communication (i.e., SICU computer to CCU computer) and data transfer from the CCU computer to the physicians discussion station.

The initial SICU system consists of a single small computer and four bedside monitoring stations.

The following is a list of our basic design objectives:

(1) The Data Communication System must provide for expansion. For example, soon it will need to handle patient data and provide digital display data for a mobile data acquisition system which may be located several floors distant in the Clinical Research Center. In addition, the Data Communication System would allow for additional computer units to be added in the future and allow for data transfers to and from now unanticipated special equipment.

(2) One of our most important objectives is simplicity of protocol for intercomputer communication. Our experience indicates that a large share of the difficulty in intercomputer communication is imposed by the communication medium. The necessity for a large data buffer, retry procedures, error recovery procedures, programmed interlocks, and general hand shaking results in an unwarranted use of computer memory cycles and memory locations. A simple communication protocol would overcome these problems.

(3) Equally important is the objective of reliability. A simple, but effective protocol should help. The probability of transmitting an undetected error between computers should be extremely low, perhaps less than once per month. The probability of transmitting an undetected error from a transducer or to a display could conceivably be higher. Equipment malfunction must not disable the entire communications system. Finally the elements of the communication system should be modular and easily replaceable.

(4) The increment in cost between the computer approach and conventional monitoring devices should be relatively small, requiring that the SICU Data Communication System be modest in cost.

(5) The design should emphasize the development of a concept which permits modular expansion for not only SICU and CRC requirements, but also permits linkage to other nodes in a general hospital information system.

A system concept has been developed which satisfies the basic objectives. As hospital requirements tend to cluster units into local areas the communication system structure will consist of Local Buses and Message Shuttles. The Local Bus will utilize a parallel transmission structure and facilitate transfer rates of one megaword per second. (This provides a system capacity of approximately 250 times the average data rate required by the SICU computer system). The length of the Local Bus will be limited to about 150 feet to keep propagation times small compared to interword times. A standard interface (Local Bus Terminal) will be provided to allow bus input and output from a variety of devices. The concept of a local bus also permits some control of the noise environment to be exercised.

The Message Shuttle provides a technique for linking local buses to permit communications with remotely located data sources and sinks, i.e., Monitoring Cart for Research Environment, Coronary Care Unit Computer System, etc.

The Message Shuttle interfaces with the Local Bus through a standard Local Bus Terminal. The Shuttle will maintain power system isolation between Local Buses preventing ground loops and minimizing shock hazard.

The detailed design and development of the components for implementation of the SICU communication system is presently in progress.

D-4. A Computer System for Surgical Intensive Care

Personnel: V. W. Gerth, Jr., BCL
J. R. Cox, Jr., BCL
L. J. Thomas, M.D., BCL and Anesthesiology

Support: RR 00396
HE 10523
Washington University

A computer system for Surgical Intensive Care has been designed in accordance with the guidelines set forth previously (see PR 6, D-2 and this report D-1). A strong effort has been made to implement the required functions with high reliability at a minimum cost. The computer selected for this application is the Artronix PC-1200 (see A-1), which will provide data acquisition, processing, and display of patient parameters and abnormal conditions.

This version of the PC-1200 will have an 8K core memory and special interfaces for this application including interfaces to the Video Display System (see D-2), the Data Communication System (see D-3), and a Sample Clock to establish the time base for monitoring. The Video Display interface is used by the computer to display annotated traces of ECG and blood pressure in a non-fade form on all four patients simultaneously. In addition, alphanumeric alarm messages will be displayed through the Video Display System. A special IOT instruction is used to control the video displays. In the case of graphic information, the computer transmits a sequence of 8-bit words that represent the amplitude of the wave form at the sampled points. In the case of alphanumeric information, the computer provides a character position and character code needed by the video display system for each character to be displayed.

The Data Communication System is also interfaced to the computer with a special IOT instruction for operating the Local Bus Terminal, and is used to acquire digitized patient parameters and status information as well as to update digital readouts of patient parameters at the bedside, the nurses station, and the doctors discussion station.

D-5. Transducer and Signal Conditioners for Surgical Intensive Care

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A study has been undertaken to select physiological transducers and signal conditioners for use in the proposed Surgical Intensive Care Unit (SICU). The depth of analysis of a particular manufacturer's product was graded into several levels. The first level consisted of a study of sales brochures and discussions with manufactures' representatives. If, according to manufacture claims, a product met a minimum set of functional and technical criteria, the product was subjected to a deeper analysis involving product demonstrations, discussions with product users and study of manufacturers' technical documentation (i.e., schematics and test reports). Products surviving these first two levels were obtained for testing.

Two manufacturers' signal conditioner systems reached this final stage of evaluation. BCL Monograph 153 describes the procedure and results for the ECG amplifier tests. Hewlett-Packard 8800 series signal conditioners were selected for use in the Surgical Intensive Care Unit.

The same approach is being used for the selection of transducers. The types of transducers required by the monitoring system were defined. To each type of transducer performance specifications were assigned and testing procedures developed. Most of the testing effort has been devoted to pressure transducers because of the many new devices available in this area. Testing is still being conducted on numerous transducers and no final conclusions have been reached.

D-6. Mechanical and Architectural Considerations in a Design of a Surgical Intensive Care Unit

Personnel: R. J. Arnzen, BCL
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R. E. Clark, M.D. Surgery

Support: RR 00396
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Washington University

Within the past year mechanical and architectural planning for an intensive care unit for cardiothoracic surgery at Barnes Hospital has been brought to completion. Renovation of the unit is scheduled to commence the third week in July with completion expected some time in October.

The mechanical and architectural design of this unit has been influenced from various sources. Chief among them were human factor considerations and a desire to deliver patient care with maximum efficiency and safety.

A rectangular area 24 feet wide by 42 feet long provided approximately 1000 square feet of floor area in which to fit four patient rooms, a physicians discussion, medicine preparation, hopper, storage room, and central monitoring console. Final plans call for two patient rooms to be located at each end of the unit. Two adjacent rooms will be used to treat acute patients who have just come from surgery via an elevator located directly across a hallway from these rooms. The others will handle those patients who have graduated out of an extreme intensive care condition and have become aware of their surroundings. Acute patient rooms are divided by sliding glass partitions to permit extension of available floor space about the bedside. Graduate rooms will be partitioned by solid panels to provide visual and acoustical isolation between beds.

At the head of each patient bed the following services will be available:

Compressed air

Three vacuum sources of different pressure

Oxygen

Surgical Lighting

Two 208 v receptacles

Eight 115 v outlets (four of which will be on an emergency system)

Temperature regulated water coolant supply for thermal blankets

Coolant will be cooled or heated by means of electrically powered heat exchangers located in the wall. This system will include electrical isolation designed to eliminate shock hazards inherent in portable electric coolers.

An instrumentation package for monitoring of physiological parameters will reside at the head end of each patient bed. This package will be recessed in the wall in order that premium space about the bedside is not obstructed. A typical package will weigh approximately 150 pounds and includes a defibrilator, power supplies, analog scope, and signal conditioners for use with the central monitoring system. Transducers at the bedside will be bar mounted with their leads brought to this instrumentation package.

A monitor console will be located in the area between the acute and the graduate patient rooms. The central location of this console will permit the user to have each room in view with reasonable head movement. On one side of this area, behind the console, a medicine preparation, hopper and storage room will serve the needs of the nurse delivering patient care. A doctors discussion station will be located across the room in front of the console. Such an arrangement will separate physician activities from the nurses' high traffic area behind the central console.

Throughout the unit a 9 foot suspended acoustical ceiling will absorb sound. Tile floors, glass partitions, and washable wall covering will permit thorough scrubbing of the unit.

D-7. Experiments in Display System for Monitoring

Personnel: L. J. Thomas, M.D., BCL and Anesthesiology
R. W. Hagen, BCL

Support: RR 00396
HE 10523
Washington University

Several LINC programs were written to simulate a "moving scroll" display of digitized analog data (ECG and arterial pressure) as proposed for the SICU video display system. The programs provide for evaluation of display format, "sweep" speed, data rate and psychophysical phenomena related to video field interlace.

D-8. A Computer Simulation of Acid Base Relations

Personnel: L. J. Thomas, M.D., BCL and Anesthesiology
C. E. Molnar, Sc.D. Computer Systems Laboratory
G. C. Johns, B.S., Computer Systems Laboratory

Support: Washington University

A LINC teaching program was written to permit student examination of the physicochemical interactions of blood acid-base parameters. The program permits student manipulation of blood composition (hematocrit, CO_2, partial pressure, base excess, oxygen saturation) appropriate to examination of the consequences of varying P_{CO_2} and base excess under both aerobic and anaerobic conditions. Also, included is the option to specify the composition of arterial blood and examine the effects of varying cardiac output on the composition of mixed venous blood. The results of these manipulations are displayed graphically on the LINC scope and can be printed out in tabular form via the teletype. The following dependent variables are available for display as functions of the independent variables noted above and/or included in the printout:

1. plasma pH
2. CO_2 partial pressure
3. plasma bicarbonate concentration
4. whole blood bicarbonate concentration
5. whole blood hemoglobin net charge concentration
6. whole blood plasma protein net charge concentration
7. whole blood carbamino concentration
8. whole blood total CO_2 concentration
9. whole blood base excess concentration
10. oxygen saturation
11. cardiac output

Question and answer sequences appropriate to the student level were composed to permit unaided student manipulation of the program options via the keyboard.

During the spring semester, computer time was provided as a supplement to lectures on acid-base chemistry of the blood in the freshman physiology course at the School of Medicine. Twenty-four groups (of 4 or 5 students) were each given two hours "laboratory" time at the computer in which to complete prescribed exercises and then examine other conditions of their choice. Even though all of the groups completed the required exercises in the allocated time, approximately 20% of the class chose to use the program as a study aid on their own time.

D-9. Program Development for the Determination of Clinical Parameters from Blood Gas Measurements

Personnel: L. J. Thomas, M.D., BCL and Anesthesiology

Support: RR 00396
HE 10523
Washington University

Algorithms have been developed and programmed for calculating clinically useful blood parameters from laboratory data including pH, P_{CO_2}, PO_2, hematocrit, plasma protein concentration and the patient and blood gas analyser temperatures. Calculated values include blood buffer base, base excess, oxygen saturation for both analyser and patient temperatures; and values for pH, P_{CO_2} and PO_2 corrected to patient temperature. In most cases the necessary relationships have been taken from the literature but the PO_2 temperature conversion required new expressions. The algorithms have been tested by comparing computed values with those obtained by conventional laboratory techniques and established nomograms using blood obtained in clinical situations. The excellent agreement obtained justifies plans to apply these algorithms in the computer assisted monitoring system under development for the SICU.

D-10. Design of a Monitoring Cart for Use in Research Environments

Personnel: J. R. Cox, Jr., BCL
R. W. Hagen, BCL

Support: RR 00396

The design of the monitoring system for the SICU incorporates a flexible communication system (see D-3). Because of requirements for computer monitoring in the Clinical Research Center, several floors distant from the SICU, a mobile monitoring cart is under design that communicates with the computer using wide band digital techniques. As presently planned the cart will monitor the physiological variables that have been selected for the SICU (see PR 6, D-2) and connect easily to the communication system at any one of a number of remote sites. Video displays of computer output will be available on the cart.

D-11. <u>Noise Measurements on Digital Signal Transmission Systems</u>

Personnel: G. J. Blaine, BCL

Support: RR 00396
Washington University

The increasing use of computers to monitor the critically ill, to automate clinical laboratory tests and to implement hospital information systems demonstrates the need to provide communication of digital data within the hospital complex.

Many design alternatives are available for the transmission of digital data. Proper selection of a technique for a particular installation requires knowledge of the communication channel noise to achieve a reasonable balance between reliability of transmission and system costs.

An investigation was initiated to determine the severity of electrical noise on transmission cables along typical paths within the hospital. The first phase of the investigations is to determine the number of noise pulses which exceed the thresholds of typical digital receivers. This is accomplished on a rather coarse basis by an adjustable threshold comparator and a pulse counter. Data is logged on a daily basis. Three coaxial cables are presently monitored:

(1) Surgical Intensive Care Unit (100 feet),

(2) Catheterization Lab (100 feet), and

(3) Cardiac Care Unit to Biomedical Computer Lab (2185 feet).

Preliminary results indicate pulses exceed typical integrated circuit receiver thresholds (1.2 volts) hundreds of times per day on cable (3), hundreds of times per week on cable (2) and less than a hundred times per week on cable (1).

The next phase of investigation will consist of a more detailed examination of the noise; finer temporal resolution and perhaps interarrival statistics.

D-12. Computer Applications in the Cardiac Catheterization Laboratory

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J. M. Pexa, BCL
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During the past year, the system of Programmed Console programs for cardiac catheterization data analysis has been in operation in the Barnes Hospital cardiac catheterization laboratory on a routine basis. Data has now been collected and analyzed on over 200 patients. In addition, a number of utility programs that allow the storage and retrieval of data have been written. Numerous modifications to the original programs have been implemented. As a result of these studies, it is clear that the current system is a feasible one and its utility is underscored by the frequency with which cardiologists depend upon it for data analysis.

Important additions to the system allow the storage of digitized data on the disc file of the IBM 360/50, with archival storage on industry compatible magnetic tapes. Additional programs allow the retrieval from magnetic tape of the complete data from a single patient by supplying an IBM 360/50 program with the patient's name and catheterization number. The data, when transmitted to the Programmed Console by telephone lines is written locally on cassette tape and may then be manipulated in the usual fashion.

Another feature of the current system allows the filing on a tape of patients and their diagnoses. Subsequent retrieval of patients meeting certain logical conditions is possible. For example, patients who have mitral stenosis or mitral insufficiency but who do not have aortic valve disease can be found. Such searching has generally clinical utility as well as value for research.

D-13. Shaft Rotation Transducer for Prosthetic Heart Valve Tester

Personnel: R. W. Hagen, BCL
R. E. Clark, M.D., Surgery

Support: RR 00396
HE 13803
Washington University

The Shaft Rotation Transducer is used to convert shaft rotation into an integral number of pulses by interrupting the optical path between a small incandescent light source and a silicon photodiode. The sensor drives an amplifier which provides a square pulse train input to a digital counter. By gating the digital counter on for a known time period the shaft rotation rate can be obtained directly from the counter readout.

The optical path is interrupted by a shaft mounted nonreflective protrusion. The rotation transducer permits an accurate measurement of the number of pumping cycles which the prosthetic heart valve, under test, has experienced.

D-14. Signal and Power Distribution in a Cardiothoracic Operating Room

Personnel: R. W. Hagen, BCL
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R. E. Clark, M.D., Surgery

Support: RR 00396
Barnes Hospital
Washington University

The renovation of a cardiothoracic operating room was complete in the Fall of 1970. The monitoring system consists of six modular signal conditioners, two 17-inch display scopes, a light beam recorder and three digital displays. An isolation transformer powers all components of the monitoring system.

Initial operation revealed unacceptable noise levels on all scope displays as well as hazardous electrical potentials between various "isolated" ground points. A careful study of the system disclosed numerous unintentional ground loops and interconnections between "isolated" patient ground and power neutral. The power system problems were solved by rerouting and reconnecting the offending ground wires. Currently the monitoring system is operating satisfactorily.

D-15. Optical Blood Level Sensor for an Oxygenator

Personnel: R. W. Hagen, BCL
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Support: RR 00396
Barnes Hospital
Washington University

The optical blood level sensor is used to sound an alert for the attending technician when the level of blood in the oxygenator reservoir drops below a preset point during open heart procedures. The sensor is a cadmium sulfide cell mounted at the end of a small diameter cable which is attached to a control unit. Within the control unit is a battery, a sensitivity control and the audible alerting device. During operation the sensing cell is attached to the outside of the translucent oxygenator reservoir at an appropriate level. When the oxygenated blood within the reservoir drops below this level the unit senses the change in light level and sounds the alert. The device has been operating satisfactorily for about six months.

E-1. Teleprocessing Programs

Personnel: E. Van Patten, BCL
R. H. Greenfield, BCL

Support: RR 00396

Use of the collaborative data processing facilities has increased steadily, but slowly, over the past year. It does not yet strain the present hardware configuration of four data lines connecting up to ten remote Programmed Consoles and LINC's to the IBM 360/50.

IBM 360/50 Communications. The most radical change that was made this past year in the 360 program (see PR 5, E-3, PR 6, E-1) has been the implementation of a method of retaining the summaries of line usage. These summaries, which include the totals (per line) of the messages transmitted, of timeouts, of hardware errors, and of bad transmissions (usually caused by line interference), provide a day-by-day record of the extent and reliability of the system's use.

Upon normal termination of the 360 program these statistics, covering the interval during which the program had been running, are written to the HASP log and so are printed as part of the standard output. Any abnormal termination (such as ABEND, a cancellation of the program, or a 360 failure) normally results in the loss of these totals. To circumvent this problem, the statistics and the time are written every five minutes onto a short sequential disk file called LOGBKUP. An end marker is written at the beginning of the file when the program is ENDed, but not when it is abnormally terminated. In the latter case then, the last written statistics are available when the communications program is next started. At this time they are copied onto the HASP log for later printout and the starting time for the next interval is written onto the file. The file is not reinitiated until a normal termination occurs so that successive "blows" of the 360 will result in additional sets of these totals being retained on LOGBKUP.

Weekly and monthly summaries are made of the transactions and errors for each line in correlation with the length of time each of the remote terminals has a data line selected. These summaries are a reliable aid in determining the trends of usage of the 360 communications.

Several minor additions have also been made. An option has been added to the RUN function so that when all the members belong to the same file the file name need be specified only once. A console command "CLEAR" has been included which will remove a file name from the files-in-use list, maintained to prevent more than one user from simultaneously writing into a single file (see PR 5, E-3). The purpose of this console command is to release a file that is trapped on this list by a data line failure, or by the premature abandonment of a PUT, GTPT, or COPY request. The START and STOP console commands have been expanded to allow a specified data line to be started or stopped.

Another addition to the 360 program is the facility to investigate error conditions which usually cause a program to be terminated, and to prevent such termination when it is possible for normal operation to resume. A specific case involves writing into a file that is already full. This does not affect other users manipulating different files, so the offending file name is put into the files-in-use list and program operation is resumed. The handling of other error conditions will be added as the need arises.

Release 19 of Operating System 360 was put in use in March of this year. Changes in IOS (Input Output Supervisor) and BTAM (Basic Telecommunications Access Method) caused some problems which have not yet been completely resolved. Meanwhile we are still using the Release 17 BTAM module.

BCL Monograph 104 details the collaborative mode processing programs that run in the IBM 360/50. This monograph has been revised to include the changes and additions made to the system during the last two years [(1)]. The program listings are now printed separately and are available in BCL Monograph 104B [(2)].

(1) D. Bridger, "Collaborative Mode PC Support Using OS/360," BCL Monograph 104, Revised April, 1971.

(2) D. Bridger, "Manuscript Listings - Collaborative Mode PC Support Using OS/360," BCL Monograph 104B, April, 1971.

E-2. Interfacing a PDP-12 for Collaborative Data Processing

Personnel: R. L. Hill, BCL
E. Van Patten, BCL

Support: RR 00396

An interface has been designed to establish communication between a PDP-12 in the Nuclear Medicine Division and the IBM 360/50 through the switching system described in PR 5, E-1. Standard IOT instructions are used to transfer eight bit words to and from the interface and to check the status of the interface. The necessary serial/parallel conversion between the interface and the telephone line is achieved with the use of teletype transmitter and receiver logic cards manufactured by Digital Equipment Corporation. A communication subroutine written for the LINC and described in PR 5, E-3 has been converted to run on the PDP-12.

E-3. Switching System for Collaborative Data Processing

Personnel: R. H. Greenfield, BCL
H. D. Ambos, BCL
P. S. Berger, BCL
G. J. Blaine, BCL
V. W. Gerth, Jr. BCL

Support: RR 00396

The computer switching system which has been reported on in previous progress reports (PR 5, E-6 and PR 4, E-1) has undergone minor engineering updating while remaining in service during the past year. These changes are: 1) An expansion of the number of remote computers regularly connected to the system to a total of nine. The present system capacity is ten. 2) A replacement of reed relay decoders with solid state contactless decoders. This latter change increased system reliability and required the redesign of the translator circuits which interface the decoders to the crossbar digital logic. 3) Several pen and ink recorders (PR 5, E-7), which were used to monitor the IBM 360 availability and to monitor the usage of the switching system by the remote computers, were replaced with one 30 channel electric recorder. This change reduced the time required to set up the monitoring and to analyse the record.

Preliminary work on the expansion of the system to handle an additional ten remote computers, yielding a total system capacity of twenty, has been started.

E-4. Robustness of Protocols Used in Computer Networks

Personnel: A. Ichijo, BCL
J. R. Cox, Jr., BCL

Support: RR 00396
Washington University

The data communications protocol used in a computer network is a system of equipment and programs that determines the sequence of steps carried out by participating computers under all circumstances of normal operation and during recovery from errors whether the source be transmission noise, operator mistakes, or incorrect higher level programs. A robust protocol always recovers automatically from an error. Less robust protocols may result in excessive calls to the computer operator or even complete system failure.

A theoretical investigation was undertaken of the robustness of a protocol as indicated by the operator call rate. Errors were limited to those introduced by transmission noise. Each possible sequence of STEPS must be analysed for both single-bit and multiple-bit errors in transmission.

The Washington University protocol[1] was analysed in detail and the results compared with measured operator call data[2]. The protocol analysis appears to explain the observed data and in addition indicates the direction for improvements and simplifications.

The most effective single step appears to be the increase in the number of retries allowed before the operator is called. This number has, until now, been arbitrarily set at three, but an order of magnitude increase in robustness can apparently be obtained by doubling this limit. An experiment to test this conjecture is planned.

(1) G. J. Blaine, H. D. Ambos, and V. W. Gerth, Jr., "Switching System for Inter-Computer Communication," BCL Monograph No. 123, Sept., 1969.

(2) A. Ichijo, "Robustness of Protocols Used in Computer Networks," Washington University, St. Louis, Missouri, 1971 (M.Sc. Dissertation).

F-1. Computer Analysis of Plasma Fibrinogen Chromatograms

Personnel: A. P. Fletcher, M.D., Medicine
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L. Roy, Medicine

Support: RR 00396
FDA 70-55
HE 03745
HE 04814
Washington University

Plasma fibrinogen chromatography is a method whereby the relative proportions and nature of the fibrinogen complexes, fibrinogen itself, and fibrinogen derivatives may be quantified in plasma. The method has been shown to provide unique information at the clinical level, since it documents the presence or absence of *in vivo* thrombosis, intravascular coagulation, or fibrinolytic states.

While the use of large chromatographic columns provides discrete resolution of the various fibrinogen complexes, derivatives, and fibrinogen itself, such methods are impractical for clinical studies because of their time-consuming and intensely laborious nature. Consequently, for clinical studies, relatively small Biogel 5M columns (0.9 x 60 cm) are used to provide results in a single working day. Under such conditions, discrete resolution of the various fibrinogen fractions is not obtained and the analytic problem involves the analysis of various complex curves to determine the relative percentage of the various components isolated.

Since the elution volume of each fibrinogen complex or derivative of interest can be determined experimentally, a successful program for resolution of these complex curves has been written for the Wang 720 B Desk-Top computer and the 702 Plotting Output.

The best-fitting curve for the actual data points is first calculated by the method of least squares. The computer then solves five simultaneous equations for five defined elution volumes (shape of the individual elution curves is calculated by chromatographic plate theory) and the computer then plots the results in graphic form (702 Output) and prints chromatographic percentage composition. This program has proven to be of great utility, since it allows the expression of the results in quantitative and objective fashion.

F-2. Kinetics of Chronic Subdural Effusions

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Support: RR 00396
Washington University

Acute and chronic subdural effusions remain a common problem in the pediatric age group. Several therapeutic approaches over the years have been suggested, though none have been proven to be effective consistently, nor have they been adequately compared to the natural history of the effusion. We remain vitally interested in this problem for these reasons. Our first objective is to define accurately the volume of the subdural effusion during the time course of the disease. This will allow us to judge the efficacy of a particular therapeutic approach and also to predict whether the subdural effusion will resolve. Our second objective is to develop a model describing the kinetics of the proteins of varying molecular weight which are present in the effusion fluid. We speculate that the pathological neomembranes forming acutely around the subdural effusion are initially well vascularized with abnormally large sinusoids, permitting rather free diffusion of blood proteins into the subdural space. With passage of time, we suspect that the neomembranes gradually become less vascularized, decreasing the movement of proteins from one compartment to the other. Analysis of protein turnover rates and their respective rate constants are being investigated to validate this contention. The data are obtained by injecting ^{131}I- or ^{125}I-labeled albumin into either the subdural space or the blood followed by sampling over a period of several days. The modeling is being done with SAAM (see C-14).

A complete understanding of the changes occurring in an effusion over time would, hopefully, allow us to evaluate the techniques presently employed in the treatment of subdural effusions in children and, furthermore, would facilitate our ability to predict whether a particular subdural effusion would persist or resolve spontaneously.

F-3. Cassette Tape Storage System for the Programmed Console

Personnel: J. M. Pexa, BCL
J. R. Cox, Jr., BCL

Support: RR 00396

Several changes were made to the cassette system which was described in PR 6, F-15. The Digideck Model 60 transports were replaced by later versions. The newer units were purchased with all-solid-state read/write amplifier electronics replacing mechanical relays on the earlier versions.

This allowed improvements to be made in the software controller. The new transports were provided with a fast speed, four times faster than the normal. The earlier version had a speed ratio of three.

The software controller was rewritten to take advantage of the improved operating characteristics of the transports. The tape format was modified so that a 200-microsecond bit time is used, resulting in a total block time of 1.0 seconds. Other formatting details remain essentially the same.

The tape instruction set was revised so that only two instructions are provided, a READ GROUP instruction and a WRITE/CHECK GROUP instruction. From one to eight contiguous blocks on a tape can be referenced by one of the instructions.

The software occupies 700 (octal) contiguous core locations and also uses 10 index registers and 8 image registers during the execution of a tape instruction. The cassette routines are loaded into the PC memory via the datamaster unit.

F-4. Human Foveal Far-field Radiation Pattern

Personnel: J. M. Enoch, Ph.D, Ophthalmology
J. H. Scandrett, Ph.D., Physics

Support RR 00396
EY 00204
Washington University

Studies of retinal receptor optical properties performed on excised (and in a few cases *in vivo*)[1] preparations revealed individual rods and cones to have narrow directional transmissivity[2]. This directionality for both classes of receptors was far narrower than that which would have been predicted from psychophysical measurements of the Stiles-Crawford effect of the first kind[2,3]. However, these observations were consistent with comparable studies made on glass fiber optics elements of comparable dimensions and difference in index of refraction between core and cladding.

A means was sought to link or reconcile the two sets of findings. A far-field radiation pattern was recorded in the central fovea of a specimen. The density profile measured from a photograph of the far-field pattern was analysed with the IBM 360/50 computer-controlled optical scanner which centered on the peak of the distribution and at each of 64 intervals passing through the center of the peak. This optical technique provides a function which is somewhat similar in nature to the Stiles-Crawford distribution[4].

(1) J. M. Enoch, Comments on "Excitation of Waveguide Modes in Retinal Receptors," J. Opt. Soc. Amer. 57: 548, 1967.

(2) J. M. Enoch, "The Retina as a Fiber Optics Bundle," Appendix B in Kapany, N. S.: Fiber Optics Principles and Applications, New York, 1967, Academic Press, Inc., p. 372.

(3) W. S. Stiles, "The Directional Sensitivity of the Retina, Ann. Roy. Coll. Surg. 30: 73, 1962.

(4) J. M. Enoch and J. H. Scandrett, "Human Foveal Far-field Radiation Pattern," Inves. Ophthal., 10: 167, 1971.

F-5. Bleaching Effect on Frog Outer Segments

Personnel: J. M. Enoch, Ph.D., Ophthalmology
J. H. Scandrett, Ph.D., Physics

Support: RR 00396
EY 00204
Washington University

An infrared interference microscope was developed in order to study the effects of a white light bleach on the physical properties of single retinal receptors. The diameter and optical path length of fresh frog rod outer segments was determined before and just after a major bleach.

Following light exposure, receptor diameter increased between 2-4% and optical path length remained virtually unchanged. This caused a decrease in index of refraction and in concentration or organic solids in the outer segment. The implication is that a transfer from the surrounding aqueous immersion medium had occurred. These changes were superimposed on other events occurring in these cells.

Having knowledge of the presence of cell boundaries and the shape of the fringe, computer analysis allowed fine determinations of changes in measured parameters to be made with confidence well beyond nominal resolution limits. This analysis utilized a computer-controlled optical image scanner connected to the IBM 360/50 (see PR 4, F-4, PR 5, F-14, PR 6, F-22). Results are in press[1].

(1) J. M. Enoch and J. H. Scandrett, "A Study of the Effects of Bleaching on the Diameter and Index of Refraction of Frog Rod Outer Segments." Submitted for publication.

F-6. <u>Mass Spectrometer Application Programs</u>

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J. A. Parker, BCL

Support: RR 00396
CA 10926
GM 21863
NS 05159

The mass spectrometer PDP-12 data acquisition system (see PR 6, F-1) was further extended and put into routine use with the LKB-9000 mass spectrometer. Data is reduced on-line to a form containing the peak abundances and positions, and the positions of the mass calibration pulses. About 200 scans containing 200 peaks in the range 0-500 mass units can be stored on one tape. This is sufficient for continuous scanning of gas chromatograph effluent.

Oscilloscope displays are used to control the data collection. The threshold for detecting fragment ion peaks is set while viewing a display of noise from the spectrometer. After typing in a description of the experimental conditions, the operator can select either single or continuous scans, using the computer clock to control the scan rate. After each scan the data is displayed as a bar graph of mass abundance versus mass number, showing the precise positions of each datum. Each scan may be automatically stored on tape, or the operator may select only those scans that seem worth saving. The description and clock time is saved too. The latter may be compared with gas chromatograph retention times.

Stored data can be viewed at leisure at a rate of about one spectrum per second. The bar graph display can be enlarged by programmable computer potentiometers so that any region can be viewed in great detail. This feature is especially useful for comparing a sequence of scans, or monitoring a small peak during data acquisition. Any spectrum can be plotted with a variety of options. A more detailed description can be typed in, supplementing that stored with the spectrum. Plots can be made any size, any mass range, with special regions of enlargement of both the abundance and mass scales.

Mass calibration has been achieved to 850 mass units, with close attention to the calibration circuit. Each scan contains calibration information which is available in the form of a display of the deviations of the peak positions from the mass marker positions. Thus, calibration errors are obvious at a glance. Data is normally reduced by assigning each peak to the nearest mass marker. A more complex procedure under study will extend the mass range and provide more reliability near the upper end of the present range.

This system is in use in the Psychiatry Department at Washington University and at the laboratories of Professor Bo Holmstedt, Department of Toxicology at the Karolinska Institute in Stockholm, Dr. J. Throck Watson, Department of Pharmacology, Vanderbilt University School of Medicine, and Drs. Evan and Marjorie Horning, Institute of Lipid Research, Baylor Medical College, and is being installed at the laboratory of Dr. Per Vestergaard, Rockland State Hospital, New York.

F-7. Mass Spectrometer Research

Personnel: W. F. Holmes, BCL
T. J. Cicero, Ph.D., Psychiatry
G. R. Drysdale, Ph.D., Biochemistry
W. H. Holland, A.B., Psychiatry
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S. A. Kornfeld, M.D., Medicine
W. R. Sherman, Ph.D., Psychiatry

Support: RR 00396
CA 10926
GM 21863

The LKB-9000/PDP-12 mass spectrometer/computer system has been used for a number of investigations. A method for analysis of mono-, di-, and tri-phosphoinositides by gas chromatography was developed, using the mass spectrometer to validate the method. The technique is currently utilized for measurement of inositides in regions of the brain at the milligram-of-tissue level. During the development of the technique, it was discovered that cardiolipin can be simultaneously measured by the same procedures. The mechanism of action of flavoprotein acyl CoA dehydrogenases has been investigated using deuterated substrates to study the proton exchange reactions catalyzed by these enzymes, utilizing the isotopic rate effects caused by substituting deuterium for hydrogen. The mass spectrometer is used to measure the deuterated substrates before and after reaction with the enzyme in order to determine the rate and extent of reaction. The information is combined with spectrophotometric data to elucidate the detailed enzyme-substrate reaction mechanism. The structure of the carbohydrate portion of normal and multiple human myeloma IgG immunoglobulins has been partially determined using combined gas chromatography-mass spectrometry. The IgG glycopeptides were methylated, hydrolyzed and alditol acetates prepared and separated by gas chromatography. Mass spectrometry established the identity of each methylated sugar derivative, and thus the linkage between sugars in the intact glycopeptide.

F-8. Estimation for Mass Spectrometer Data

Personnel: D. L. Snyder, BCL
W. F. Holmes, BCL

Support: RR 00396
Washington University

Computer aided mathematical techniques are under investigation for the improvement of mass spectrometer data resolution. A typical spectral record consists of a series of pulses; the amplitude of each pulse corresponds to a mass abundance, and the shape corresponds to the response of the spectrometer to an idealized single mass line. It is sometimes difficult, if not impossible, to determine the individual amplitudes by visual inspection of the data because pulses overlap. We are currently investigating mathematical models for mass-spectrometer data. We plan to use these models with standard estimation techniques to try to resolve individual pulse amplitudes.

F-9. Fractional Mass Measurement by Peak Matching

Personnel: W. F. Holmes, BCL
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R. Hessling, Dept. of Toxicology, Karolinska Institute, Stockholm
B. Holmstedt, Dept. of Toxicology, Karolinska Institute, Stockholm
A. Linnarsson, Dept. of Toxicology, Karolinska Institute, Stockholm
L. Pierrou, Dept. of Toxicology, Karolinska Institute, Stockholm

Support: RR 00396
GM 13978

A PDP-12 computer-controlled acceleration voltage for the LKB 9000 mass spectrometer has previously been developed at the Toxicology Department of the Karolinska Institute, Stockholm, Sweden. This permits selective measurements of four fragment ions, resulting in a 100- to 1000-fold increase in sensitivity over conventional mass spectrometry. Samples as small as one nanogram can be measured quantitatively with a minimum detection in the 1 to 10 picogram range. The equipment seems capable of other new uses. In particular, it generates accurate voltage changes which can be related to an equivalent mass by the formula $\frac{M_1}{M_2} = \frac{V_2}{V_1}$. Thus the mass of an unknown fragment can be measured by comparison with a known fragment by accurately matching the peaks of the two fragments. Such measurements have been made using relay switches and potential dividers but are very slow and require large quantities of purified material. A computer controlled measurement would be suitable for use with gas chromatograph effluent, using much smaller quantities of complex mixtures, separated only by the gas chromatograph column.

Preliminary programs have been written and tested at the Karolinska Institute. A small voltage sweep is generated about the selected acceleration voltage, and the mass abundance signal displayed as a peak, with the peak center calculated after each sweep. The electronic stability of the signal seems promising. The accuracy of the method will relate to problems of peak shape and noise (see F-8), which remain to be tested after construction of the appropriate equipment here. The system will also be useful for very rapid scans over a limited mass range which is needed for quantitative isotope tracer work. Additionally, it will be useful for high resolution capillary columns. The high mass range can be considerably extended with accurate calibration, a difficult matter using magnetic scanning. A number of complex biological molecules could be measured if reliable calibration in the range 1000 to 1500 were available.

F-10. Kinetic Simulation of Glutamic Dehydrogenase

Personnel: D. J. Bates, A.B., Biochemistry
C. Frieden, Ph.D., Biochemistry
W. F. Holmes, BCL

Support: RR 00396
AM 13332
GB 26483X

A program has been written to simulate the concentration changes of intermediates in the glutamate dehydrogenase reaction:

$$E + D \rightleftharpoons ED \rightleftharpoons E'D$$

$$E'D + G \rightleftharpoons E'DG \rightleftharpoons E''DG$$

$$E''DG + D \rightleftharpoons E''D_2G \rightleftharpoons E'''D_2G$$

where E is enzyme, D is cofactor (either DPNH or TPNH) and G is the ligand GTP. The simulation became practical only after installation of the floating-point hardware on the PDP-12, as software took enormous amounts of time for the thousands of iterative changes in concentrations for each of the above intermediates. At present the program is being overhauled so that changes in the basic chemical equations can be accomplished merely by entering the new equations, and so that experimental and simulated data can be compared on the oscilloscope.

F-11. <u>Data Acquisition and Analysis of Stopped Flow Kinetic Data</u>

Personnel: D. J. Bates, A.B., Biochemistry
C. Frieden, Ph.D., Biochemistry
W. F. Holmes, BCL

Support: RR 00396
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We have started on a system designed to permit the use of the PDP-12 in the handling and reduction of data from a Durran-Gibson stopped-flow apparatus. At present we have constructed an interface between the stopped flow apparatus and a Hewlett Packard FM tape recorder for temporary storage of data, eliminating the need for on-line computer use. Programs to reduce and store the data are presently in preparation.

F-12. <u>Tissue Culture Measurements</u>

Personnel: J. H. Scandrett, Ph.D., Physics
L. J. Tolmach, Ph.D., Radiology
A. R. Zacher, Ph.D., Physics

Support: RR 00396
CA 04483

Our cell-scanning and sizing algorithm has been applied to a pilot study of automatic scanning of cancer cell colonies. Petri dishes with stained cell colonies are photographed on 35 mm film. The scanning system automatically optimizes the scanning density threshold, automatically centers on the visible field and then scans a 256 by 256 point raster, creating a packed binary core image of the cell colonies. The cell-sizing algorithm then systematically counts all colonies, forming a histogram of colony areas. The dual processor 360-PDP-11 System counts and measures 100 cell colonies in approximately 1/2 second. Comparisons between automatic dish counts and conventional human scanning are in progress.

F-13. A System for Automatic Drug Injection

Personnel: B. F. Spenner, BCL
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J. R. Cox, Jr., BCL
R. N. Tatum, BCL
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Support: RR 00396
CA 04483

This system, as described in PR 6, F-26, provides a means of automatically adding and removing solutions from Petri dishes which contain cells growing as adhering monolayers under nutrient medium. The automation of this research process provides many advantages over the manual execution of the identical process. The most important of these advantages is that the automated system facilitates the execution of long-term experimental processes. AUDRI (Automatic Drug Insertion Unit) and HERO (Helix Rotator) are the two devices which form the System for Automatic Drug Injection. AUDRI is a mechanical device operated under the control of HERO, a small process control computer (see BCL Monograph 151).

Since the last Progress Report, AUDRI and HERO have been tested as a system in all phases of operation. A program called "Translator" has been developed for use with the LINC computer. Translator allows the researcher to use a LINC computer to define an experimental process (sequence of operations) that is to be performed by HERO and AUDRI.

F-14. LINC-4 Tape Controller

Personnel: B. F. Spenner, BCL
C. R. Buerke, BCL
J. R. Cox, Jr., BCL

Support: RR 00396

The LINC-4 tape controller was designed to provide the PC (Programmed Console) with a local mass-storage device. The present PC system requires that information be transferred to or from the PC using either datamaster cards, or a mass-storage device connected to the PC by phone lines. Entering lengthy programs with datamaster cards is a slow and tedious process and therefore not attractive. Using a distant mass-storage device to transfer information is not an optimum method since it depends on the operation of both the distant mass-storage device and the telephone lines.

The LINC-4 tape controller is a functional copy of the classic LINC tape controller[1]. The two units use the identical recording technique and data format. The primary differences between the two tape controllers are listed in Table 1.

	LINC 4	Classic LINC
Logic Elements	Integrated TTL	Discrete Pulse-Level Logic
Number of Addressable Blocks	1024	512
Tape Marking Ability	No	Yes
Operation	Buffered	Unbuffered

TABLE 1

BCL Monograph 149[2] further describes the LINC-4 tape controller.

(1) S. M. Ornstein and C. E. Molnar, "Magnetic Tape System," LINC Theory of Operation II, Volume 14, September, 1966.

(2) B. F. Spenner, "A Description of the Linc-4 Tape Controller", BCL Monograph 149, March, 1971.

F-15. A Disc Storage System for Auditory Research

Personnel: B. F. Spenner, BCL
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D. A. Ronken, Ph.D., Central Institute for the Deaf

Support: RR 00396
NS 03856

A system is presently being developed which will allow an ensemble of complex auditory signals to be stored digitally on a magnetic disc. The system will also have the capability of randomly retrieving any of these stored signals on command. The system will be capable of handling anywhere from 1 to 200 discretely retrievable signals. The total signal storage time of the system will be at least 60 seconds. The completed system will be composed of three parts: the sound-to-memory unit, the memory unit, and the memory-to-sound unit.

The sound-to-memory unit will sample the analog input signal and convert it to the appropriate digital number. This digital number will then be transferred to the memory for storage. A sampling rate of 16 kHz will be used to allow signal frequencies of 8 kHz or less to be recorded and reproduced. At the present time a study is being conducted to determine if a quantized $\log_2$ data compression technique can be applied to this system (see B-14). This data compression will provide an increase in the system recording time.

The memory unit consists of a buffered 7.86 Mbit magnetic disc. The disc is equipped with a movable read/write head that accesses any one of the 240 tracks located on the disc. The worst-case time required to move the read/write head from the present track to an adjacent track is 20 ms. The buffering associated with the disc compensates for head access time when a discrete signal requires more than one track of storage.

The memory to sound unit will perform an operation which is the inverse of the operation performed by the sound to memory unit. The output of the memory to sound unit will be a reproduction of a selected signal which has been previously stored on the disc.

Two specific auditory experimental applications include:

1) Research on speech perception by normally hearing, and hearing impaired children and adults.

2) Research on auditory capabilities and auditory learning, in animals and human children and infants.

The initial system will be implemented with macromodules[1] to allow several system configurations to be conveniently tested.

(1) S. M. Ornstein, M. J. Stucki, and W. A. Clark, "A Functional Description of Macromodules," Washington University, Computer Systems Laboratory Technical Memorandum 11, December, 1966.

F-16. A Semiautomatic Wire-Wrap System

Personnel: B. F. Spenner, BCL
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C. Buerke, BCL
V. W. Gerth, Jr., BCL

Support: RR 00396

The construction of a digital logic system requires that logic elements be connected together in specified configuration. In recent years the decreased physical size of logic elements has increased the difficulty of interconnecting these elements. Semiautomatic wire wrap systems are designed to reduce this construction difficulty.

During the past year a study was performed to test the feasibility of using a semiautomatic wire-wrap system at BCL. The four points considered during the study included: the adaptability of the technicians to the system, the ease with which the system was used, wiring error rate, and operational efficiency. The study was performed by constructing a complex logic network with a semiautomatic wire wrap system. The LINC-4 tape controller (see F-14) was the system constructed during the study.

The semiautomatic wire wrap system used in this study was built with GORTH, an X-Y scanner (see PR 5, B-3), and the LINC computer. A LINC program was written for this study which allowed wiring list codes entered via the LINC keyboard to be translated into GORTH position commands.

The most useful application of the system is in the construction of several copies of the same device so that the time required for wire list entry can be spread over several units. Since most of the construction at BCL is one of a kind, the usefulness of the system is marginal.

F-17. A Computer System for a Signal Detection Laboratory

Personnel: B. F. Spenner, BCL
R. F. Kimach, Central Institute for the Deaf
C. S. Watson, Ph.D., Central Institute for the Deaf

Support: RR 00396
NS 03856

A computer system has been operating in the Signal Detection Laboratory of Central Institute for the Deaf for two years. Recent additions to the system include: a digital cassette recorder and an ADC (analog to digital converter). The cassette recorder provides a high-speed data storage and retrival system required by high data rate experiments. This cassette recorder built by Sykes Datatronics Inc., is capable of storing 3.6 million bits of information. The average access time to any of 256 storage blocks is 12 sec.

The buffered 10-bit ADC provides the system with the ability to analyze and record analog waveforms. This ADC, built by Digital Equipment Corporation, has a conversion time of 10 μs. An amplifier with selectable gain and offset was placed at the input to the ADC so that signals having a wide range of amplitudes could be accepted by the analog input.

F-18. Mathematical Models of the Mechanics of the Cochlea

Personnel: M. D. Lien, BCL
J. R. Cox, Jr., BCL

Support: RR 00396

In PR 6, F-14, a general outline of the study was given and a more detailed investigation has continued this year. The damping effect due to the viscosity of the fluid has been studied. The ratio of damping to inertial effects has been computed. This ratio is about 10 at 10 Hz and decreases to about 0.1 at 20 kHz. The displacement of the basilar membrane due to static pressure across it has also been reexamined. All parameters which appear in the governing equation can now be determined from empirical data. Putting all the pieces together, the low frequency response of the basilar membrane has been computed. Comparison with the measurements of Békésy yields rather good agreement.

F-19. Analog Transmission of the Electrocardiogram

Personnel: V. W. Gerth, Jr., BCL
F. Kunze, BCL

Support: RR 00396

On a number of occasions it has been desirable to transmit the electrocardiogram over appreciable distances for processing in the Barnes Coronory Care Unit. Bell System leased lines have been used for applications outside the hospital whereas BCL-owned cable is attractive for shorter runs. An FM modulation technique using a voltage controlled oscillator and a standard telemetering discriminator provided the required low-frequency response while maintaining compatibility with the Bell System voice grade lines.

In an effort to achieve a simpler solution, an ECG transmission system was breadboarded using monolithic integrated-circuit phase-locked loops. Two identical integrated circuits serve as the major elements of the system. One functions as a conventional phase-locked loop tuned to the channel center frequency to provide FM demodulation. The other serves as a voltage-controlled oscillator by using only that portion of the integrated circuit. The additional phase-locked loop components are not used. In this manner, a single integrated-circuit type can serve in both the transmitter and receiver. Overall system linearity and bandwidth is adequate for the ECG.

F-20. Solid-State Keyboards for Computer Input

Personnel: P. S. Berger, BCL
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V. W. Gerth, Jr., BCL
K. L. Kunkelmann, BCL

Support: RR 00396

Previous experience with solid-state keyboards (see PR 6, B-6 and F-17) indicates greatly improved reliability over that experienced with electromechanical types. As a result, the experimental solid state keyboard for the LINC has been replaced by a fully encoded design developed in collaboration with the Computer Systems Laboratory and now commerically available from the Microswitch Division of Honeywell. The three classic LINC's belonging to BCL now use this keyboard.

The keys operate without contacts using a solid-state Hall-effect detection scheme and amplifier contained in the key. An interface to the LINC has been constructed which stores the key code until requested by the computer. As with the mechanical equivalent, the solid-state keyboard interface clears the key code when so directed and reports the clear status back to the computer. Circuitry is included to prevent error if two keys are depressed simultaneously. Plans are near completion to install a single printed circuit card inside the keyboard so that it will then be a direct plug replacement for its mechanical counterpart.

Preliminary design has been completed for a similar keyboard to be used on the PC as a replacement for the existing electromechanical version. It will be fully encoded using the PC keyboard code.

F-21. A Study of X-Ray Film Retrieval Traffic

Personnel: N. J. Falvey, B.S., Information Processing Center
V. W. Gerth, Jr., BCL

Support: RR 00396
Washington University

A detailed profile of scheduled diagnostic x-ray examinations was needed for planning purposes. The data was available in paper tape form, but with a nonstandard code and many noncontent-bearing characters. A LINC program was written to delete the unwanted characters and transform the data to BCD code. The output was then stored on industry-compatible tape using the LINC-Datamec facility at BCL. These tapes, representing over 9,000 records, were then processed for the study at the Information Processing Center.

F-22. Digital Computer Analysis of Pulmonary Function Studies

Personnel: N. J. Falvey, B.S., Information Processing Center
V. W. Gerth, Jr., BCL

Support: RR 00396
HE 10237

The computer analysis of pulmonary function studies reported previously (PR 6, F-27) has been continued. Additional data has been acquired and processed using the programs developed previously. Minor engineering improvements have been made to the LINC-Datamec interface to improve reliability.

F-23. Mathematical Model of Sr-90 Activity in Permanent Teeth

Personnel: R. Wette, D.Sc., Biostatistics
M. M. McCrate, B.S., Biostatistics
H. L. Rosenthal, Ph.D., Physiological Chemistry (Dental School)

Support: FR 00396
Washington University

Computer programs were developed for testing mathematical models to represent the relationship between the specific activity of Sr-90 in the crowns and roots of extracted permanent bicuspid teeth and the Sr-90 content of the food (milk) available during tooth development. A file was created for ready retrieval of the over 400 data points, each consisting of the birth year, sex, age at extraction and the specific activity of crowns and roots retropolated for radioactive decay from date of analysis to that of extraction. A four point Lagrange interpolation was performed on the Sr-90 activities of the (annual and semi-annual) metropolitan milk samples for point-to-point time-matching with the tooth data. The first model applied to the data assumes that the concentration (specific activity) C(T) of Sr-90 in the crown or root, respectively, of a tooth extracted at age T is equal to

$$C(T) = k \cdot \Sigma f(h_i) \cdot S(t_i) \cdot \exp[-b \cdot (T-t_i)],$$

where $S(t_i)$ is the specific activity (concentration) of Sr-90 in the food (milk) at time t_i, $f(h_i)$ is the mineral incorporation rate or "feeder function" (mass incorporated per mass of tooth) of the tooth at age h_i, b is a rate constant representing radioactive decay and possible irreversible turnover of Sr-90. The summation extends over positive values of the feeder function f(h), and k is an arbitrary proportionality factor. A rectangular and a symmetrical triangular feeder function have been tried so far. A crude test of the model was performed by computing and plotting the product-moment and intraclass cross-correlation coefficients between (the logarithms of) the observed Sr-90 activities and the C(T) values obtained for various widths of f(h) and for consecutive half-year positions of the mid-point of f(h). It was found that within a reasonable range of widths of both rectangular and triangular f(h) and of values for b (.025 to .075 for crowns and .075 to .125 for roots), the primary maximum of the correlation coefficient appeared when the midpoint of the mineral feeder function was at an age of about 4 years for crowns and 9 years for roots. This agrees with the knowledge that crowns and roots are formed around these ages on the average.

F-24. Statistical Tests for Homogeneity of Variances Among Samples of Correlated Normal Variables

Personnel: R. Wette, D.Sc., Biostatistics
S. C. Choi, Ph.D., Biostatistics

Support: RR 00396
Washington University

The variance-ratio F-test for the comparison of two variances (e.g., comparison of the precision of two methods of measurement) is invalid when the two samples are point-wise correlated (e.g., both methods of measurement performed on same unit). A test for this case first suggested by Pitman and Moore and modified and extended by the authors was investigated with respect to its performance. Its power function depends on the correlation between the paired data points and is analytically intractable. A second-order approximation to the power function was computed numerically for various alternatives (in terms of the variance ratio) and correlation coefficients. Also, the critical values were computed numerically for the modified (and more easily applicable) test over a range of rejection regions and sample sizes.

F-25. Development, Modification, and Implementation of Computer Programs for Statistical Analysis in Problem-Oriented Biomedical Applications

Personnel: R. Wette, D.Sc., Biostatistics
M. M. McCrate, B.S., Biostatistics

Support: RR 00396
Washington University

In many biomedical and clinical applications, standard statistical methods such as available in computer-systems-supported application packages are not useful since they are ineffective or invalid for the type of problem encountered. A library of biomedically and clinically problem-oriented (but within this area, general-purpose type) applications computer programs have been developed and implemented as card decks or users library load modules. Examples are: Parameter estimation in singular and arbitrarily censored passage-time distributions; Resolution of mixed and arbitrarily censored nominal distributions; Wilcoxon-Gehan two-sample test for censored observations; G-test for goodness-of-fit and heterogeneity with small samples; Modifications of program package routines to provide non-standard output; Assembler language subroutines for random number generation, logical operations, assay moving, etc.; Additivity test for analysis of variance.

F-26. Single Crystal X-ray Studies of Enzymes

Personnel: L. J. Banaszak, Ph.D., Biochemistry

Support: RR 00396
GB 27437X
GM 13925
Washington University

These studies are aimed at obtaining the molecular structure of enzymes from cardiac muscle cells. The long range goal is to understand the biochemical mechanism and control of these catalysts in terms of their molecular structure. In the last year, the main effort centered around the structure of the cytoplasmic form of malate dehydrogenase. A 3.0 Å resolution electron density map has now been obtained and current work now involves trying to place about 7,000 atoms into this map.

To calculate the map, approximately 1.5 million numbers (115,000 x-ray reflections) were measured. The measuring instrument (x-ray diffractometer) punched these results on paper tape. The data were transferred from punched paper tape to Linc tape and then using LINCOMM, the numbers were sent to the IBM 360/50 for further processing. The total technician time used to transfer all these data was only about 30 hours.

Fast Fourier programs were used for the calculation of the 3.0 Å electron density map, reducing the computational time by at least a factor of five over conventional techniques.

VI. TRAINING ACTIVITIES

During the year the Biomedical Computer Laboratory engaged in the following training activities:

Course in LINC and PC Programming, Fall, 1970

This course was taught by Michael D. McDonald and included binary arithmetic and coding in both machine language and assembly language. Attending the course were:

Carole A. Benbassat, B.S.	Radiology
Richard G. Boguslaw, B.S.	Dental Student
Linda L. Eby, B.A.	Computer Systems Laboratory
Memory P. F. Elvin-Lewis, Ph.D.	Dental Microbiology
Ronald W. Hagen, M.S.	BCL
Harrison Bradley Keller	Medical Student
Robert E. Kleiger, M.D.	Cardiology, Jewish Hospital
Kenneth Kunklemann	BCL
Harland Leinberger, B.S.	Dental Student
Judel Lew, B.A.	Dental Student
Michael Leslie Matheny, B.S.	Radiology
Jon F. Moran, B.A.	Medical Student
Gerald L. Palagallo, M.D.	Radiology
Carl F. Pieper, B.S.	BCL
Michael C. Rigden, B.A.	Psychology
Kenneth L. Ripley, B.A.	Psychology
Robert A. Sind	Physiology
Frank L. Tobey, Jr., Ph.D.	Opthalmology
Allen B. Weiner, Phar.D.	Medical Student
Kelly Williams	Psychology

Course in LINC and PC Programming, Spring, 1971

This course was also taught by Michael D. McDonald with the same content as the Fall course. Attending the course were:

Chung-Kwang Chou, B.S.	EE Graduate Student
Eugene R. Hoff, M.D.	Pathology
Michael H. M. Huang, B.S.	EE Graduate Student
George F. Keyser, M.S.	Biomedical Engineering Graduate Student
Michael D. Loberg, B.S.	Radiology
Gary F. Plazyk	Applied Mathematics and Computer Science
Raj Kumar Sehgal, Ph.D.	Psychiatry
Maria L. Straatmann, B.A.	Radiology
Alan J. Tiefenbrunn, A.B.	Medical Student
Trieu-Kien Truong, B.S.	EE Graduate Student
Rhung-Fan Wang, M.S.	Applied Mathematics and Computer Science
Jacek Wiecko, Ph.D.	Psychiatry

VII. SEMINARS

During the year the following seminars were sponsored by the Biomedical Computer Laboratory:

"The Use of Computers for the Evaluation of Regional Pulmonary Function" July 23, 1970	Dr. Merle K. Loken Department of Radiology University of Minnesota Hospitals Minneapolis, Minnesota
"Physical Aspects of Nuclear Medicine" August 13, 1970	Dr. Kenneth B. Larson Biomedical Computer Laboratory Washington University School of Medicine St. Louis, Missouri
"Object Enhancement and Extraction; A Review" September 24, 1970	Judith M. S. Prewitt Department of Radiology University of Pennsylvania Philadelphia, Pennsylvania
"Clinical Evaluation of Premature Beat Detection by Digital Computer" October 30, 1970	Dr. G. Charles Oliver Department of Medicine Washington University School of Medicine St. Louis, Missouri
"Analysis of Regional Cerebral Blood Flow Made with A Non-Diffusible Indicator" November 13, 1970	Dr. Bernard Hoop, Jr. Physics Research Laboratory Massachusetts General Hospital Boston, Massachusetts
"New Concepts in the Field of Thrombosis" November 20, 1970	Dr. Anthony P. Fletcher Department of Medicine Washington University School of Medicine St. Louis, Missouri
"Current Status of Biomedical Laser Applications" December 4, 1970	R. James Rockwell, Jr. Directing Physicist Laser Laboratory Children's Hospital Research Foundation Cincinnati, Ohio

* "The Applications of Operations Research Techniques to the Planning of Medical Care Delivery"
December 15, 1970

John D. Thompson
Professor of Public Health and Associate Dean for Planning
Yale University School of Medicine
New Haven, Connecticut

"Rate, Volume and Permeability Information Derivable from Multiple Tracer Kinetic Curves"
March 26, 1971

Dr. William Perl
Department of Medicine
College of Medicine and Dentistry of New Jersey
Newark, New Jersey

"Surgical Intensive Care Computer Applications"
April 21, 1971

Dr. Louis C. Sheppard
Department of Surgery and Department of Information Sciences
University of Alabama Medical Center
Birmingham, Alabama

** "Computer Synthesis of Speech"
May 12, 1971

James L. Flanagan
Acoustics Research Department
Bell Telephone Laboratories
Murray Hill, New Jersey

** "Studies of Speech through Synthesis"
May 13, 1971

Noriko Umeda and Cecil H. Coker
Acoustics Research Department
Bell Telephone Laboratories
Murray Hill, New Jersey

"Computerized Patient Record for a Cardiac Intensive Care Unit"
May 28, 1971

Dr. Harry A. Fozzard
Department of Medicine
University of Chicago
Chicago, Illinois

"A Time-Shared Medical Information System on a Mini-Computer"
June 11, 1971

Peter Schwenn
Department of Gynecology and Obstetrics
University of Wisconsin Medical Center
Madison, Wisconsin

* Seminar sponsored by Technology in Health Care Program and Department of Applied Mathematics and Computer Science, Washington University

** Seminar sponsored jointly with Central Institute for the Deaf

VIII. PAPERS, PUBLICATIONS AND ORAL PRESENTATIONS

Cox, J. R. and Logue, R. D., "Some Observations on the Economics of Computer Systems for Monitoring Electrocardiographic Rhythms," to be published in Computers in Biomedical Research.

Elliott, L. L., "Pitch Memory for Short Tones," Perception and Psychophysics, Vol. 8, pp 379-384, 1970.

Enoch, J. M. and Scandrett, J. H., "Human Foveal Far-Field Radiation Pattern," Investigative Ophthalmology, Vol. 10, No. 3, pp 167-170, March, 1971.

Finn, A. L. and Rockoff, M. L., "The Kinetics of Sodium Transport in the Toad Bladder, I. Determination of the Transport Pool," The Journal of General Physiology, Vol. 57, No. 3, pp 326-348, 1971.

Hill, R. L. and Cox, J. R., "A Gamma Camera Interface to a Small Computer," presented at the Symposium on the Sharing of Computer Programs and Technology in Nuclear Medicine, Oak Ridge, Tennessee, April 2-3, 1971.

Hill, R. L. and Cox, J. R., "A System of Programs for a Small Computer Interfaced to a Gamma Camera," presented at the Symposium on the Sharing of Computer Programs and Technology in Nuclear Medicine, Oak Ridge, Tennessee, April 2-3, 1971.

Holmes, W. F., "A Display Oriented Mass Spectrometer-Computer System," to be published in Analytical Chemistry.

Ichijo, A., "Robustness of Protocols Used in Computer Networks," Washington University, St. Louis, Missouri, 1971 (M.Sc. Dissertation).

Larson, K. B. and Cox, J. R., editors, "Computer Processing of Dynamic Images from an Anger Scintillation Camera," Volume I, Workshop Proceedings, Biomedical Computer Laboratory and Mallinckrodt Institute of Radiology, School of Medicine, Washington University, St. Louis, Missouri, January, 1971.

Larson, K. B. and King, T. B., "Reduction of Data and Propagation of Errors in the Capillary-Reservoir Method of Measuring Diffusion Coefficients in Liquids," submitted for publication to Metallurgical Transactions.

Larson, K. B., Snyder, D. L. and Eichling, J. O., "Measurement of Blood Flow by External Monitoring of Radiotracers with Interference Due to Recirculation and Perfusion of Adjacent Tissues," to be submitted for publication to Circulation Research.

Mast, T. E., "A Study of Signal Units of the Cochlear Nucleus of the Chinchilla," Journal of Acoustical Society of America, Vol. 48, pp 505-512, 1970.

Miller, J. D., "Audibility Curve of the Chinchilla," Journal of Acoustical Society of America, Vol. 48, pp 513-523, 1970.

Nolle, F. M. and Clark, K. W., "Detection of Premature Ventricular Contractions Using an Algorithm for Cataloging QRS Complexes," presented at the San Diego Biomedical Symposium, March, 1971.

Oliver, G. C., Nolle, F. M., Wolff, G. A., Cox, J. R. and Ambos, H.D., "Detection of Premature Ventricular Contractions with a Clinical System for Monitoring Electrocardiographic Rhythms." To be published in Computers in Biomedical Research.

Peters, P. E., Ter-Pogossian, M. M., Rockoff, M. L., Metzger, J. M. and Koehler, P. R., "Measurement of Renal Blood Flow by Means of Radioactive Water Labeled with Oxygen-15", presented at the International Symposium on Radionuclides in Nephrology, New York, January, 1971. To be published in the proceedings of this meeting.

Pexa, J. M., "A Cassette Storage System for the Programmed Console," Washington University, St. Louis, Missouri, 1971 (M.Sc. Dissertation).

Roberts, G. W., Larson, K. B. and Spaeth, E. E., "The Interpretation of Data from Tracer Kinetic Experiments." To be submitted for publication to Bulletin of Mathematical Biophysics.

Snyder, D. L., "Filtering and Detection for Doubly-Stochastic Poisson Processes." Accepted for publication in IEEE Transactions on Information Theory.

Snyder, D. L., "Filtering for Independent Poisson Processes Having Stochastic Intensity Functions." Presented at the Mervin J. Kelly Communications Conference, University of Missouri, Rolla, October, 1970.

Snyder, D. L., "Information Processing of Scintillation Data Obtained in Nuclear Medicine." Presented at IEEE St. Louis Section of ICCC, Washington University, St. Louis, May, 1971.

Snyder, D. L., "Parameter Estimation for Radioactive Tracer Data." Presented at the Mervin J. Kelly Communications Conference, University of Missouri, Rolla, October, 1970.

Snyder, D. L., "A Separation Theorem for the Detection of Doubly-Stochastic Poisson Processes." Proceedings of the Fifth Annual Conference on Information Sciences and Systems, Princeton University, Princeton, New Jersey, March, 1971.

Snyder, D. L. and Collins, L. D., "Realization of Filter-Squarer Receivers," IEEE Transactions on Information Theory, Vol. IT-17, No. 1, pp 97-101, January, 1971.

Snyder, D. L. and Rhodes, I. B., "Bounds on the Accuracy in Causal Filtering for Nonlinear Observations with Some Implications on Asymptotic Separation in Stochastic Control, Report No. CSSE-719, School of Engineering and Applied Science, Washington University, St. Louis, Missouri, June, 1971.

Spenner, B., "Hero, A Small Process Control Computer," Washington University, St. Louis, Missouri, 1971 (M.Sc. Dissertation).

Thomas, L. J., Roos, A., Glaeser, D. H., and Cox, J. R., "Pulmonary Blood Flow Response to Cyclic Inflation of Cat Lungs", to be published in American Journal of Physiology.