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Progress Report No. 8

Biomedical Computer Laboratory

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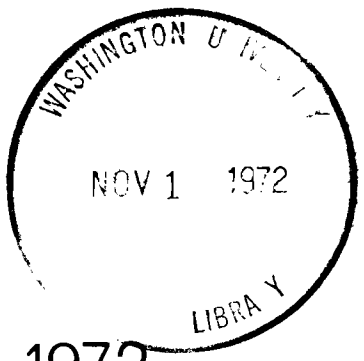
PROGRESS REPORT

No. 8



1 July 1971 - 30 June 1972

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

BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

PROGRESS REPORT NO. 8

1 July 1971 - 30 June 1972

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I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes work done during the period from July 1, 1971 through June 30, 1972. 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 investigator's laboratories to BCL by means of either analog tape recordings or telephone lines and, more frequently, by taking the computers to the investigator's 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 Model 50 at the Washington University Computing Facilities.

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 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, the Vice Chancellor for Medical Affairs, the Vice Chancellor for Research, and the Director of the University Computing Facilities.

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 Dr. W. S. C. Chang, 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 of the Biomedical Computer Laboratory and Computer Systems Laboratory under the NIH Biotechnology Research Resources grant. During the past year the Committee 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 Committee meets periodically with the WUCL Coordinating Committee to review developing techniques and to advise upon desirable areas of applications.

*Resignations submitted during the year. Replacements to be appointed shortly.

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

Partial support was received by the laboratory for a training program in Health Care Technology:

HS 00074 Technology and Health Care

A new contract to study the relationship of arrhythmias and sudden death sponsored by the National Heart and Lung Institute was begun in collaboration with the Department of Medicine and the Jewish Hospital:

NIH-71-2481 Sudden Cardiac Death and the Onset of Myocardial Infarction

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

AM 10591 Metabolism of Islets of Langerhans and Hormone Release

AM 13332 Metabolic Regulation and Interacting Enzyme Systems

CA 04483 Effects of X-Ray on Normal and Malignant Cells

CA 05139 Training in Radiation Therapy Physics and Biology

CA 10702 Mathematic Biology of Neoplastic Growth

CA 10926 Use of Heavy Isotopes in Biological Research

CA 13053 Clinical Cancer Radiation Therapy Research Center Grant

GM 01311 Training Program in Biochemistry

GM 01747 Training Program in Radiology (Nuclear Medicine)

GM 01827 Training Program for Engineering Biophysics

GM 13925	Structural Studies on Malate Dehydrogenase
GM 14357	Structural Studies on Enzyme Proteins
GM 17386	Scanner Computer Analysis of Radiographic Bone Images
HL 00082	Clinical and Experimental Research in Respiration
HL 05332	Medical Cardiology - Graduate Training Program
HL 11034	Circulatory Regulation and Myocardial Contractions
HL 13803	Development of a Trileaflet Aortic Valve Prosthesis
HL 13851	Cyclotron Produced Isotopes in Biology and Medicine
HL 14147	Special Center of Research in Thrombosis
NS 03856	Auditory Communication and its Disorders
NS 05522	Neuroradiology Training Grant
NS 06833	An Interdisciplinary Stroke Program
NS 07498	Peripheral Auditory Mechanisms
RR 05389	General Research Support
RR 05491	General Support Fund
RR 06115	Health Science Advancement Award

Atomic Energy Commission:

AT(11-1)-1653	Biologic Considerations in Anatomic Imaging with Radionuclides
AT(11-1)-2011	A Method for the Determination of Regional Blood Flow in Tissues by Means of Stimulated X-Ray Flourescence

Air Force Office of Scientific Research and Development:

F 44620	Control Guidance and Information Fundamentals of Aerospace

Health Services and Mental Health Administration:

MH 07081	Research Training - Biological Sciences
MH 20717	Morphine Tolerance and High Sensitivity Measurement
RM 00056	Cooperative Regional Radiation Therapy Development and Support Program

Kellogg Foundation

Life Insurance Medical Research Grant:

G70-26	Structural Studies on Heart Malate Dehydrogenases

Metropolitan Life Insurance

National Science Foundation:

GB-26483X	Enzyme Structure and Function
GB-27437X	X-Ray Structural Studies of Cytoplasmic Malate Dehydrogenase
GK-32239	Information Processing for Doubly-Stochastic Poisson Processes

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

R. Martin Arthur, Ph.D., Electrical Engineering, since June 1, 1971*
William F. Holmes, Ph.D., Biochemistry
Maxine L. Rockoff, Ph.D., Applied Mathematics and Computer Science
Lewis J. Thomas, M.D., Anesthesiology*

Research Instructor

Kenneth B. Larson, Ph.D.

Senior Research Fellow

Roger H. Secker-Walker, M.D.*

Post Doctoral Fellows

Edward L. Morofsky, Ph.D., since February 1, 1972
Joan T. Zimmerman, Ph.D., since January 1, 1972

Research Assistants

Robert J. Arnzen, Ph.D.*
James M. Baker, B.S.
Carole Ann Benbassat, B.S.
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.
A. Maynard Engebretson, D.Sc., since January 10, 1972*

Robert H. Greenfield, M.S.
Ronald W. Hagen, M.S.*
Rexford L. Hill, III, M.S.
Richard E. Hitchens, B.S., since June 5, 1972
Sung-Cheng Huang, M.S.
Monte D. Lien, M.S.
W. Edward Long, M.S., since August 1, 1971
Michael D. McDonald, B.S.
Joanne Markham, B.A.*
Nizar A. Mullani, B.S.
Floyd M. Nolle, M.S.
James M. Pexa, M.S.
Carl F. Pieper, B.S.
Shirley J. Smith, M.S.
Bruce F. Spenner, M.S.
Robert N. Tatum, B.S.
Elizabeth Van Patten, B.A.

Technical Assistants

Reginald D. Bruss, B.S., since January 24, 1972
Betty J. Greenwood
Alan Lipschultz, B.S., since September 15, 1971
James B. Minard
Emil D. Scheifler

Programming Assistant

John A. Parker, M.D.

Engineering Assistant

H. Dieter Ambos

Electronics Technicians

Daniel J. Bax, since September 28, 1971
Charles R. Buerke
Christopher R. Fraction
Joseph G. Green, Jr., since August 2, 1971
Kenneth L. Kunkelmann
Thomas F. Schuessler, B.S., since April 3, 1972

Machinist

Kenneth J. Spraul

Librarian

Gwenyth A. Loughner, M.L.S.*

Business Manager

Virginia M. Bixon, B.S.

Secretaries

Viviane D. McKay*
Wanda J. Meek
Linda Russo
Sandra Sfondouris
Linda C. Stites, since June 9, 1972

*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:

Carole Ann Benbassat, terminated September 8, 1971
Reginald D. Bruss, terminated March 25, 1972
Carol S. Coble, terminated April 24, 1972
Christopher R. Fraction, terminated September 30, 1971
Alan Lipschultz, terminated May 31, 1972
Wanda J. Meek, terminated June 28, 1972
John A. Parker, terminated July 31, 1971
Maxine L. Rockoff, terminated July 23, 1971
Shirley J. Smith, terminated September 30, 1971
Roger H. Secker-Walker, terminated September 30, 1971

Summer Personnel

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

Donald R. Bassman, B.A., Summer, 1972
William H. Cloud, Jr., B.S., Summer, 1972
Terrence J. Coleman, Summer, 1972
Ola-Olu A. Daini, B.A., Summer, 1972
Donald E. Gayou, Summer, 1972
Ronald Inselberg, Summer, 1971, 1972
William R. Lang, B.S., Summer, 1972
James W. Oetting, Summer, 1972
Jeffrey F. Painter, Summer, 1971
John A. Ritter, Summer, 1972
Robert W. Scheifler, Summer, 1972
James B. Sellinger, Summer, 1972
Mark D. Sutton, Summer, 1972
Alan J. Tiefenbrunn, B.A., Summer, 1971
Louis J. West, Summer, 1971
Hildegard C. Wette, Summer, 1972

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
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
B. A. Bohne, Ph.D., Otolaryngology
H. A. Bomze, M.S., Preventive Medicine
W. S. C. Chang, Ph.D., Electrical Engineering
S. C. Choi, Ph.D., Biostatistics
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
R. G. Evens, M.D., Radiology
N. J. Falvey, B.S., Information Processing Center
A. Feldman, Ph.D., Radiology
J. D. Ferrario, B.S., Radiology
P. Fishman, M.S., Applied Mathematics and Computer Science
H. Fotenos, Radiology
C. Frieden, Ph.D., Biochemistry
N. Glassman, B.S., Radiology
S. Goldring, M.D., Neurosurgery
R. O. Gregory, D.Sc., Electrical Engineering
G. S. Grisbeck, M.S., Physics
R. L. Grubb, Jr., M.D. Radiology
J. Hecht, A.B. Radiology
E. Hill, Ph.D., Biochemistry
R. M. Hochmuth, Ph.D., Chemical Engineering
W. H. Holland, A.B., Psychiatry
S. R. Holmes, A.B., Biochemistry
L. Jarett, M.D., Pathology
L. I. Kahn, M.D., Preventive Medicine
I. N. Katz, Ph.D., Applied Mathematics and Computer Science
R. E. Kleiger, M.D. Medicine
S. Lang, Ph.D., Physiology and Biophysics
G. R. Little, Ph.D., Electrical Engineering
M. M. McCrate, B.S., Biostatistics

T. F. Martin, M.D., Medicine
F. S. Mathews, Ph.D., Physiology and Biophysics
F. Matschinsky, M.D., Pharmacology
J. C. Metzger, M.A., Radiology
C. E. Molnar, Sc.D., Computer Systems Laboratory
G. C. Oliver, Jr., M.D., Medicine
D. Pennington, Radiology
G. T. Perkoff, M.D., Preventive Medicine
P. E. Peters, M.D., Radiology
R. R. Pfeiffer, Ph.D., Electrical Engineering
M. E. Phelps, Ph.D., Radiology
W. F. Pickard, Ph.D., Electrical Engineering
E. J. Potchen, M.D., Radiology
W. E. Powers, M.D., Radiology
M. E. Raichle, M.D., Radiology
L. Resnick, M.D., Radiology
R. E. Rider, Ph.D., Physics
G. W. Roberts, Sc.D., Chemical Engineering
E. Rodin, Ph.D., Applied Mathematics and Computer Science
A. Roos, M.D., Anesthesiology
R. S. Rosenfeld, M.D., Medicine
N. Schad, M.D., Radiology
J. H. Scandrett, Ph.D., Physics
W. R. Sherman, Ph.D., Psychiatry
B. L. Shore, B.S., Applied Mathematics and Computer Science
B. A. Siegel, M.D., Radiology
E. E. Spaeth, Ph.D., Chemical Engineering
J. S. Strauss, Ph.D., Computing Facilities
S. P. Sutera, Ph.D., Mechanical and Aerospace 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
L. Webb, Ph.D., Biochemistry
H. J. Weiss, B.S., Applied Mathematics and Computer Science
P. H. Weiss, M.D., Radiology
M. J. Welch, Ph.D., Radiology
C. S. Weldon, M.D., Surgery
R. Wette, D.Sc., Biostatistics
G. R. Weygandt, M.D., Anesthesiology
M. A. Whitney, Ph.D., Preventive Medicine
G. A. Wolff, M.D., Medicine
A. R. Zacher, Ph.D., Physics

M. D. Anderson Hospital and Tumor Institute, Houston, Texas

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

Barnes Hospital, St. Louis, Missouri

R. Adams
K. F. Bemberg
M. Evans

Central Institute for the Deaf, St. Louis, Missouri

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

George Washington University, Washington, D. C.

S. D. Rockoff, M.D.
J. R. Whiteman, M.D.

Jewish Hospital, St. Louis, Missouri

D. G. Hagenlocher
R. J. Krone, M.D.
B. A. Sandefur

Johns Hopkins University, Baltimore, Maryland

K. L. Zierler, M.D.

Methodist Hospital, Houston, Texas

M. E. DeBakey, M.D.
D. H. Glaeser, Sc.D.

National Cancer Institute, Bethesda, Maryland

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

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.

Southern Illinois University, Carbondale, Illinois

W. E. Wright, D.Sc.

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.

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 Model 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. In 1972, five new PC-1200 Programmed Consoles manufactured by Artronix, Inc. were installed at BCL in support of a variety of new and existing projects.

An IBM System 7 was installed at the laboratory in April, 1972 to become a major component of a system for the high speed analysis of electrocardiograms. 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 seven 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 Model 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 feet of specially designed space within the unit. Key BCL staff members occupy 260 square feet of office space nearby.

V. RESEARCH PROJECTS

Summary

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 equipment 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 focus in one of these project areas.

A. Radiation Therapy. The Programmed Console (PC) developed at BCL has been extensively used for radiation treatment planning. In many centers quantitative treatment planning with computerized records is an established procedure either with the PC, its successor the Artronix PC-1200, or with a similar system produced by Digital Equipment Corporation, the RAD-8. With the anticipated installation of PC-1200 computers in four of the five institutions participating in the PC evaluation program we are making plans for the establishment of a new project for patient information handling and retrospective evaluation. The project is expected to develop at two levels, a national data base, and a local patient information entry and filing system. The teleprocessing capability of the PC will be used for communication among the various participants.

B. Electrocardiographic Rhythm Monitoring. For the past two and a half years the Argus computer system for continuous ECG rhythm monitoring has been in operation at the Barnes Hospital Coronary Care Unit. Previous evaluation of the technical performance of the system left unanswered the extent of its impact on the patterns of care in the Unit. Accordingly, a group of 40 patients were assigned randomly to either a study group or a control group to compare therapy actions taken by the nursing staff with and without computer monitoring available to them. Results showed a significant increase in the use of lidocaine because ventricular arrhythmias were detected by the computer system which would have otherwise been missed.

A multiple-patient arrhythmia monitoring system using the Argus algorithms and developed by Mennen-Greatbatch Electronics, Incorporated has been installed in a community hospital. Plans for a prospective medical evaluation of the clinical import of the system at that community hospital are underway.

A study has begun to investigate the causes of sudden cardiac death through a better understanding of the role played by arrhythmias. A system is under development for the high speed analysis of tape recorded data from

ambulatory subjects in whom the presence of coronary artery disease has been documented by a recent myocardial infarction. This system, which will be able to analyze tapes played back at 60 times their recording speed, is based upon a combination of a macromodular preprocessor and an IBM System/7 computer. The basic Argus algorithms, now well tested, will be used but an interactive processing and display system will allow human editing of computer generated results.

C. Regional Tracer Kinetics. The connection of gamma-ray cameras to digital computers in recent years has been stimulated by the anticipation of a variety of important new diagnostic procedures utilizing radiopharmaceuticals. The proceedings of a workshop held in January 1971 were published last year in preliminary form and are now being edited for hard cover publication by the Society of Nuclear Medicine. In addition to development of a computer system for regional tracer kinetics, described in these proceedings, we have been working actively on mathematical models that would help us understand the data obtained with this system. An important recent result is the development of a new technique for measuring hemodynamic parameters by residue detection in the presence of radiotracer recirculation. This model accounts for added contributions to detector response due to recirculating tracer passing not only through the organ of interest but also through adjacent perfused tissue. Central to the model is the use of two injections of tracer, one at the arterial inflow and the other at the venous outflow of the particular vasculature of interest. The model has been employed successfully for measuring relative blood flow and relative blood volume in a number of experiments and diagnostic clinical procedures.

A continuing development of efficient computer techniques for processing radioisotope tracer data relies on maximum-likelihood parameter-estimation techniques. This work appears to be particularly useful in low count-rate circumstances.

Clinical application of the computer systems that we have developed continues with the estimation of such varied physiological quantities as cerebral and myocardial blood flow, cerebral glucose utilization, cerebral blood volume, ventilation and perfusion in the lung, cardiac ejection fraction, kidney function, liver function and gastric emptying.

D. Monitoring the Critically Ill. A new surgical intensive care unit (SICU) has been completed and monitoring equipment for each of the four beds in the unit installed. The digital computer portion of the system is being assembled at the Biomedical Computer Laboratory using test signals sent by cable from the SICU. A digital communication system between the patients' beds, the monitoring computer and several display stations is being assembled and tested. Plans call for high-speed communication links between the SICU, the Coronary Care Unit and the General Clinical Research Center.

E. Communications for Information Processing. Expansion of the switching system that links a network of ten small computers to the University's IBM 360 Model 50 has been deferred. Although pressures for more connections to the network have grown, uncertainty about the future of the host computer at the University's Information Processing Center has delayed this expansion. Revision of the teleprocessing programs to increase the efficiency and ease of use has been completed. Our communications efforts have branched out to include studies of multipair transmission lines used in the SICU, design procedures for binary communication over telephone lines and the development of solid-state optical digital communication system. In the future we expect to emphasize wide-band communication reflecting our anticipation of future needs in medical information processing.

F. Cardiac Catheterization Laboratory. A computer system for the Mallinckrodt Cardiac Catheterization Laboratory has been in use for more than a year and data have been collected with this system on over 400 patients. The experience gained has lead to the development of an improved version of the system that provides for self-explanatory laboratory reports, a smoother functional description of the system, a modular program structure and improved peripheral devices for the system. Commercial availability of the system is expected in early 1973.

G. Biochemical Kinetics and Mass Spectrometry. An interactive program has been developed for the simulation of the kinetics of single and multienzyme systems, using biochemical equations for input. The kinetic curves are displayed along with the experimental data, so that the investigator can revise the simulation parameters to try to improve the data fit. The program allows a more quantitative analysis of complex kinetic curves, which should aid in a more detailed understanding of enzyme mechanisms.

The gas chromatograph-mass spectrometer computer system has been in routine use for a year and a half, allowing this rapid and specific analytical technique to be applied to a number of new investigations. A high speed high voltage switching system near completion will allow for determining picogram quantities of biochemical and drugs, and greatly increase the accuracy when measuring stable isotope tracer incorporation.

H. Speech and Hearing. Work on a mathematical model of the mechanics of the cochlea has resulted in a more complete theory that promises to give insight into the cochlear response to complex stimuli. Parallel with this development, interest in digital speech synthesis at the Central Institute for the Deaf has grown. Merger of these two lines of work allows us to learn more about both speech and hearing by observing the cochlear response to synthesized speech through the use of digital computer models. Work toward these ends has begun with the development of a random access programmer for complex audio signals (RAP-1), a system for generalized waveform generation, and preliminary work on a speech synthesis.

I. Health Care Technology. During the past year the laboratory has participated in a new training grant from the Health Services and Mental Health Administration for the education of graduate engineers in health care technology. To provide a computing environment for these trainees MUMPS (Massachusetts General Hospital Utility Multiprogramming Systems) has been implemented on the PC-1200. In collaboration with the Washington University Medical Care Group we have begun several information processing activities including the development of an automated patient encounter form. During the summer of 1972, eight of the trainees participated in a three-month internship program to acquaint them with the activities of various hospital departments and to identify areas in which the application of their technical skills would be productive.

J. Other Applications of Computers. A number of our projects do not fit the previous nine categories, but are pursued because of their inherent special interest or because they may in the future develop into one of the laboratory's major areas of activity. During the past year two such activities have been identified and they are reported separately in Sections G and H. Several of the reports in this section have received only minor support from the laboratory with their major support derived from other departments.

Individual Projects

A-1. Information Handling in Radiation Therapy

Personnel: W. F. Holmes, BCL
J. R. Cox, Jr., BCL
V. W. Gerth, Jr., BCL
W. E. Powers, M.D., Radiology

Support: RR 00396
CA 05139
CA 13053
RM 00056

The Programmed Console (PC) developed at BCL has been extensively used for radiation treatment planning. An updated version with tape units, the Artronix PC-1200, has become commercially available in the last year (see PR 7, A-1), raising the total number of PC's used in radiation therapy to eighteen. Now that quantitative treatment planning with computerized records is an established procedure, the time seemed ripe for establishing retrospective studies using such treatment records to evaluate alternative methods of radiation therapy. Each member of the PC evaluation group has independently established some type of patient information system using a local large computer. Thus a considerable body of patient information is being collected which can only be compared if a common data base can be established. Four of the original five members of the PC evaluation group (Tufts, New England Medical Center, M. D. Anderson Hospital and Tumor Institute, Temple University Health Sciences Center, and Washington University Medical Center) have agreed to join a new project for patient information handling and retrospective evaluation. A common data base will be established on a large computer with national access by telephone lines, tentatively the McDonnell Douglas Automation Center's IBM 360/195 in St. Louis. The PC-1200 will be used as a remote terminal to gain access to the national computer, as well as access to the local large computer at each treatment center. The participants in this project are exchanging their old PC's for a PC-1200, and are purchasing additional memory, a large storage oscilloscope, and a telecommunication interface.

The project is expected to develop at two levels, a national data base, and a local patient information entry and filing system. The national data base could in principal become the nucleus of a larger data base with more contributors, especially other radiotherapy centers with PC-1200's. The local information system, residing in the PC-1200, will be built around the MUMPS programming language (see I-2), which has been especially designed for flexible information handling. The radiation treatment planning records will be

merged with a comprehensive data entry and filing system suitable for radiotherapy centers. Programs will be developed for data interconversion and transmission between the PC-1200, the local large computer, and the national computer.

A-2. Programmed Console User's Meeting

Personnel: B. J. Greenwood, BCL
J. R. Cox, Jr., BCL
V. W. Gerth, Jr., BCL
E. Van Patten, BCL

Support: RR 00396

The annual PC User's Meeting was held in Houston, Texas, on July 6, 1971. Proceedings began with presentation by the users of brief summaries of PC activities at their institutions during the past year. Following delivery of the reports, Artronix, Inc., outlined their development of the PC-1200, elaborating on its features and describing problem areas in the old PC that were eliminated in the new design. At the conclusion of a demonstration of the new PC the first portion of the meeting was brought to a close.

The second half of the gathering began with a summary of other uses of the PC at BCL and was followed by a general discussion of new and old business. It was decided to continue holding yearly PC User's Meetings, around the time of the American Association of Physicists in Medicine meeting, the next one to be held in Philadelphia in the summer of 1972.

The following institutions were represented at the meeting: M. D. Anderson Hospital and Tumor Institute, Houston, Texas; Medical College of South Carolina, Charleston, South Carolina; Mercy Hospital, Pittsburgh, Pennsylvania; National Cancer Institute, Bethesda, Maryland; New England Medical Center Hospitals, Boston, Massachusetts; Ontario Cancer Institute, Toronto, Canada; Stanford University School of Medicine, Palo Alto, California; Temple University Hospital, Philadelphia, Pennsylvania; University of Minnesota Health Science Center, Minneapolis, Minnesota; University of Southern California, Los Angeles, California; University of Tennessee, Memphis, Tennessee; Washington University School of Medicine, Mallinckrodt Institute of Radiology, Biomedical Computer Laboratory, St. Louis, Missouri.

Commercial groups represented were: Artronix, Inc., St. Louis, Missouri; Contemporary Science, Inc., Mt. Prospect, Illinois.

A-3. A Computer-Controlled Dose Plotter

Personnel: A. L. Bodicky, BCL
A. J. Demidecki, M.S., Radiology
A. Feldman, Ph.D., Radiology
N. Glassman, B.S., Radiology
D. Pennington, Radiology

Support: RR 00396
CA 13053
RM 00056

Several revisions are being made to the existing system (see PR 5, B-3) enabling the electronics to be concentrated on one mobile table so that shorter cables between the Dose Plotter and its remote electronics can be achieved. Other revisions consist of simplification of connections, the incorporation of a position indicating signal for the probe, and filter network for the dose rate signal. The plotters mechanical members have been reoriented to facilitate positioning with relation to the beam of the radiation generating machine. Construction and wiring in accordance with the revised design is underway.

B-1. An Evaluation of the Clinical Impact of Argus

Personnel: G. C. Oliver, M.D., Medicine
H. D. Ambos, BCL
K. W. Clark, BCL
J. R. Cox, Jr., BCL
F. M. Nolle, BCL
A. J. Tiefenbrunn, BCL

Support: RR 00396
Barnes Hospital
Washington University

For the past two and one-half years, the Argus computer system for continuous ECG rhythm monitoring has been in operation at the Barnes Hospital Coronary Care Unit. The performance of this system has been previously evaluated (see PR 7, B-1). Left unanswered has been the impact of such a computer system upon patterns of care in a modern coronary care unit. To evaluate this, a prospective study was carried out. Patients admitted during a two months period to the Barnes Coronary Care Unit were assigned randomly to either group A, a study group, or group B, a blind or control group. There were 20 patients in each group. As soon as possible after entry, each patient was continuously monitored by Argus for an average of 32 hours per patient, resulting in 1,278 hours of computer monitoring. Conventional hardware monitoring of average heart rate and monitoring by nurse oscilloscope surveillance was also done on all patients. Argus detected premature ventricular contractions (PVCs) and calculated their rate of occurrence. When Argus detected certain combinations of PVCs such as ventricular tachycardia, ventricular bigeminy, or frequent PVCs, an ECG printout of the rhythm disturbance generating the alarm was activated. Identical procedures were carried out for groups A and B with the following exception. For patients in group B, the computer generated displays and alarm strips were withheld from the nurses and physicians. In these patients, treatment decisions were based entirely on conventional monitoring.

A detailed review of nurses' notes was made to document any changes in anti-arrhythmic therapy during the period of monitoring. A treatment action was defined to be one of the following: 1) lidocaine given intravenously (I.V.) by bolus, 2) the initiation of a lidocaine drip, 3) an increase in the I.V. infusion rate of lidocaine, 4) I.V. atropine, 5) I.V pronestyl, or, 6) a chest thump. Forty-one treatment actions were taken during the course of the study. Thirty occurred in group A patients in which computer alarms were furnished and eleven in group B patients in which alarms were not furnished. In group A, an average of 3.75 actions were taken per patient with an average of 1.8 actions in group B ($p < 0.01$). The major difference noted between the two groups was increased use of lidocaine bolus in the alarm group (10 versus 2, $p < 0.05$).

It is clear that continuous ECG monitoring by digital computer, even in a well staffed unit, resulted in a significant increase in the use of lidocaine because ventricular arrhythmias were detected by the computer

system which otherwise would have been missed. During this study, no deaths occurred in either group so that the impact of such a monitoring system on mortality was not settled.

Further study, preferably in other units, will be needed to determine whether or not continuous computer monitoring will reduce mortality rate in coronary care units by reducing the incidence of primary ventricular fibrillation. Such a study is currently being planned (see B-7).

B-2. Documentation of Argus

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

Support: RR 00396
71-2481
Washington University

The Argus system of digital computer programs and equipment for monitoring ECG rhythms in cardiac intensive care unit patients has been under development at Washington University since November of 1964 (see PR 1, A-22). During the evolution of the Argus algorithms several reports have been published to describe their operation. A recent summary of the processing algorithms has now been reported(1). In addition, flow charts for the Primitive and Cycle processors have been produced to aid development of the high speed ECG analysis system (see B-5) and the commercial version of Argus (see B-7). A comprehensive description of the evolution and present status of the Argus programs and equipment as well as directions for future development has also been recently finished(2).

(1) J. R. Cox, Jr. and F. M. Nolle, "Arrhythmia Monitoring Algorithms for Real Time Applications," Proceedings of the Fifth Hawaii International Conference on Systems Sciences-Computers in Biomedicine, Honolulu, 120-122, 1972.

(2) F. M. Nolle, "Argus, A Clinical Computer System for Monitoring Electrocardiographic Rhythms," D.Sc. Dissertation, Washington University, 1972.

B-3. Advanced Clustering Techniques for the QRS Families of Argus

Personnel: F. M. Nolle, BCL
W. E. Wright, D.Sc., Southern Illinois University

Support: RR 00396

The Cycle processor of Argus clusters every QRS complex described by four morphology features (duration, height, offset, and area) in a family of similar complexes enclosed by a four-dimensional box. Hundreds of such QRS families are formed over the course of a day as newer families with slightly different features supplant older, outdated families. The present Argus algorithms also perform an elementary clustering of QRS families to identify those considered normal for the patient. For quantitative analysis of long ECG records, such as is needed for research purposes (see B-5 and B-6), additional clustering techniques for all families of QRS complexes need to be developed.

One method for more advanced clustering of QRS families using a gravitational technique has been investigated[1]. Data for this investigation consisted of the average features and total population for each of several hundred QRS families occurring in 8 hours of a patient's ECG. Several clustering parameters were tried and the combinations produced at several levels of iteration were compared with the results of manually performed clustering of representative waveforms for each family. The initial results seem quite promising so long as a human can help make crucial decisions such as the stage at which the clustering should be terminated. Additional testing of advanced clustering techniques using some human interaction will be required for development of the high speed ECG analysis system (see B-5).

[1] W. E. Wright, "A Formalization of Cluster Analysis, and Gravitational Clustering," D.Sc. Dissertation, Washington University, 1972.

B-4. Relationship of Ventricular Arrhythmias to Sudden Death -- Ambulatory Monitoring

Personnel: G. C. Oliver, M.D., Medicine
U. T. Aker, M.D., Medicine
H. D. Ambos, BCL
K. W. Clark, BCL
J. R. Cox, Jr., BCL
V. W. Gerth, BCL
D. G. Hagenlocher, Jewish Hospital
R. E. Kleiger, M.D., Jewish Hospital
R. J. Krone, M.D., Jewish Hospital
T. F. Martin, M.D. Medicine
F. M. Nolle, BCL
B. A. Sandefur, Jewish Hospital
D. L. Snyder, BCL
R. Wette, D.Sc., Biostatistics
G. A. Wolff, M.D., Medicine

Support: 71-2481
RR 00396
HE 11034
Barnes Hospital
Jewish Hospital

Sudden death is a problem of enormous magnitude in this country. It has become clear that the phenomenon of sudden death is primarily one which occurs outside the hospital environment. The background for sudden death is almost invariably coronary artery disease. Despite this, a recent heart attack is usually not found when autopsies are performed. This finding has of necessity led to the assumption that sudden death is due to a ventricular arrhythmia. The basis for the arrhythmia is presumably myocardial ischemia. A key unsolved problem is the identification of the prospective victim. The presence of coronary artery disease is a virtual necessity for sudden death, but in itself is not a sufficiently powerful predictor since the mortality rate for people with coronary artery disease, otherwise not selected, is only about 4% per year. Even though this number seems large, if all patients with coronary artery disease were treated by an agent designed to prevent sudden death, it is clear that most patients would be unduly subjected to some additional risk.

We have made the assumption that individuals who die suddenly will demonstrate serious ventricular arrhythmias while ambulatory. In order to investigate this, we have set up a protocol for monitoring patients with known coronary disease and a control group, selected to be free of disease, as they go about their normal activities. Patients selected are those who have survived a myocardial infarction and have been discharged from the coronary care units of Barnes Hospital or Jewish Hospital. The control group is a group of workers who on careful screening have no coronary artery disease risk factors. Members of both groups carry with them a small, portable tape

recorder which records their electrocardiogram for a period of 10-24 hours. For the study patients, the ECG recording is repeated for a total of ten times during the year following their release from the hospital to enable us to study the stability of arrhythmia patterns as well as their frequency. A massive data analysis task is involved in this study. A computer system for the semi-automatic recognition of ventricular arrhythmias at 60 times real time is being developed and is described in the next section (B-5).

B-5. Relationship of Ventricular Arrhythmias to Sudden Death -- High Speed ECG Analysis System

Personnel: F. M. Nolle, BCL
H. D. Ambos, BCL
K. W. Clark, BCL
J. R. Cox, Jr., BCL
O. L. Daini, BCL
V. W. Gerth, Jr., BCL
C. F. Peiper, BCL
J. A. Ritter, BCL

Support: 71-2481
RR 00396

The only practical method at present for studying the occurrence of arrhythmias in the ambulatory population involves usage of a portable tape recorder. Analysis of the tapes has been performed by manual scanning of the ECG played back at high speed, usually 60 times real time (see PR 7, B-7). However, the resultant data is highly qualitative. Moreover, we have found that significant events such as short runs of ventricular tachycardia are often missed completely by manual scanning. This latter finding has been obtained by analyzing tapes in real time with Argus.

In order to provide an accurate, quantitative picture of ventricular arrhythmias occurring in ambulatory patients, a special version of the Argus rhythm monitoring system is being developed for analysis of the recorded tapes. To handle the great volume of tapes collected in the study of ventricular arrhythmias and sudden death (see B-4), the system is designed to analyze tape recorded ECGs played back at up to 60 times real time. Since 60 times real time analysis requires processing a new sample every 33 microseconds, a hardware implementation of a portion of the initial Argus processing stages is necessary. Also, since research needs may differ somewhat from the clinical goals for which Argus was developed, a macromodular hardware implementation, coupled to a modern high-speed digital computer, offers the greatest promise for attaining the necessary processing speed with developmental flexibility. A considerable effort has already been undertaken to demonstrate the feasibility of using macromodules for this purpose (see PR 7, B-9 and B-10).

An IBM System/7 computer has been selected as the central processor for the high speed ECG rhythm analysis system. The System/7 has a 400 ns solid state memory and emitter coupled logic levels which are compatible with those of macromodules. The machine also has four priority interrupt levels with separate hardware registers for each level and a number of its instructions require only one memory cycle, thus allowing very rapid execution of program segments for which timing is crucial. The System/7 computer with 8K of memory (IBM model 5010-A8 central processor) was installed at BCL in April of 1972. A moveable head disc and disc interface were added to the system two months later. Two industry compatible tape drives (Pertec, 9 tra 45 inches per second, 800 bits per inch, 10 1/2 inch reels) with buffered formatters (dual 512 byte buffers for each) have also been delivered. In addition, a storage oscilloscope display terminal and hard copy unit (Tektronix 4010 and 4610) have been ordered and will be delivered shortly. To allow interim checkout of some peripherals concurrent with the design of permanent interfaces to the direct control channel of the System/7, a general purpose digital input/output module (IBM Multifunction Module 5012) has been obtained on temporary lease. The extremely rapid delivery of the System/7 computer has allowed us to bypass an earlier plan to construct an interim processor using macromodules to store Aztec data on digital tape and to further process these tapes with a temporary, PC-1200 computer system.

One tape drive has been interfaced to the System/7 multifunction modul and is currently being tested. An interface to a classic LINC computer located adjacent to the System/7 has also been constructed. The paper tape oriented assembler for the System/7 has been modified to allow more rapid assembly of programs using this connection to the LINC.

Work has proceeded on coding the Primitive and Cycle processor algorithms of Argus for the System/7. The LINC interface is also being used for this work to supply Aztec data from LINC tape for testing purposes. Advanced System/7 software making extensive use of macro commands for progra preparation has also been obtained and installed on the IBM 360 Model 50 system at the Washington University Information Processing Center. The existing Model 50 communications interface to the LINC (see PR 5, E-1) allow the resulting object code to be loaded into the System/7. In addition, a pre-release of the System/7 disc operating system software will be received shortly, in July of 1972.

The operation of the high speed ECG analysis system may be divided into two phases. In the first phase, as shown in Figure 1, ECG tapes are played back at 60 times real time from the analog playback unit. The sample ECG data is converted to Aztec by the macromodular preprocessor. The Primit and Cycle algorithms of the Argus computer system operate in the System/7 central processor to produce a condensed stream of data for storage on the disc. This data stream describes the exact timing of each QRS complex, its morphology classification (normal, abnormal, or borderline), its PVC classification, and a serial number identifying its membership in a family of QRS complexes of similar shape. Each family of QRS complexes is described by attributes including its total population, the average shape characteristics (duration, height, offset, and area) of its members, and a segment of Aztec

data for reconstructing a typical QRS member. A variety of other information is also present in the data stream stored on the disc (see PR 7, B-3).

The on-line processing display will use a high speed, large screen oscilloscope showing the individual members of each QRS family as they occur. For this purpose, each family will appear at a different location on the screen, thus giving a concise summary of the operation of the high speed system at any instant in time. Finally, one of the two digital magnetic tape drives will provide temporary storage for the sampled ECG for subsequent reconstruction of selected ECG episodes during the second phase of analysis.

Following the procedure shown in Figure 1 (which will take just n minutes for an ECG tape of n hours duration), the data stored on disc is retrieved for review by the technician operating the system as shown in Figure 2. Using the storage oscilloscope and hard copy unit terminal, the operator will be asked to verify the various clusterings of QRS families performed by the system. In this manner, the superior pattern recognition capabilities of the human may be employed to rectify occasional erroneous groupings of QRS families and also to screen out any remaining artifact. The operator may also request ECG paper records for unusual or illustrative segments as well as for episodes of significant arrhythmias detected by the analysis system. For this purpose, the sampled data for the appropriate segment is retrieved from the digital tape drive serving as temporary storage. Summary data presentations, such as are described in section B-6, will then be presented for hard copy records. Finally, a variety of archival data will be saved on the second digital tape drive in sufficient detail to allow any necessary re-editing of the records after review by a cardiologist.

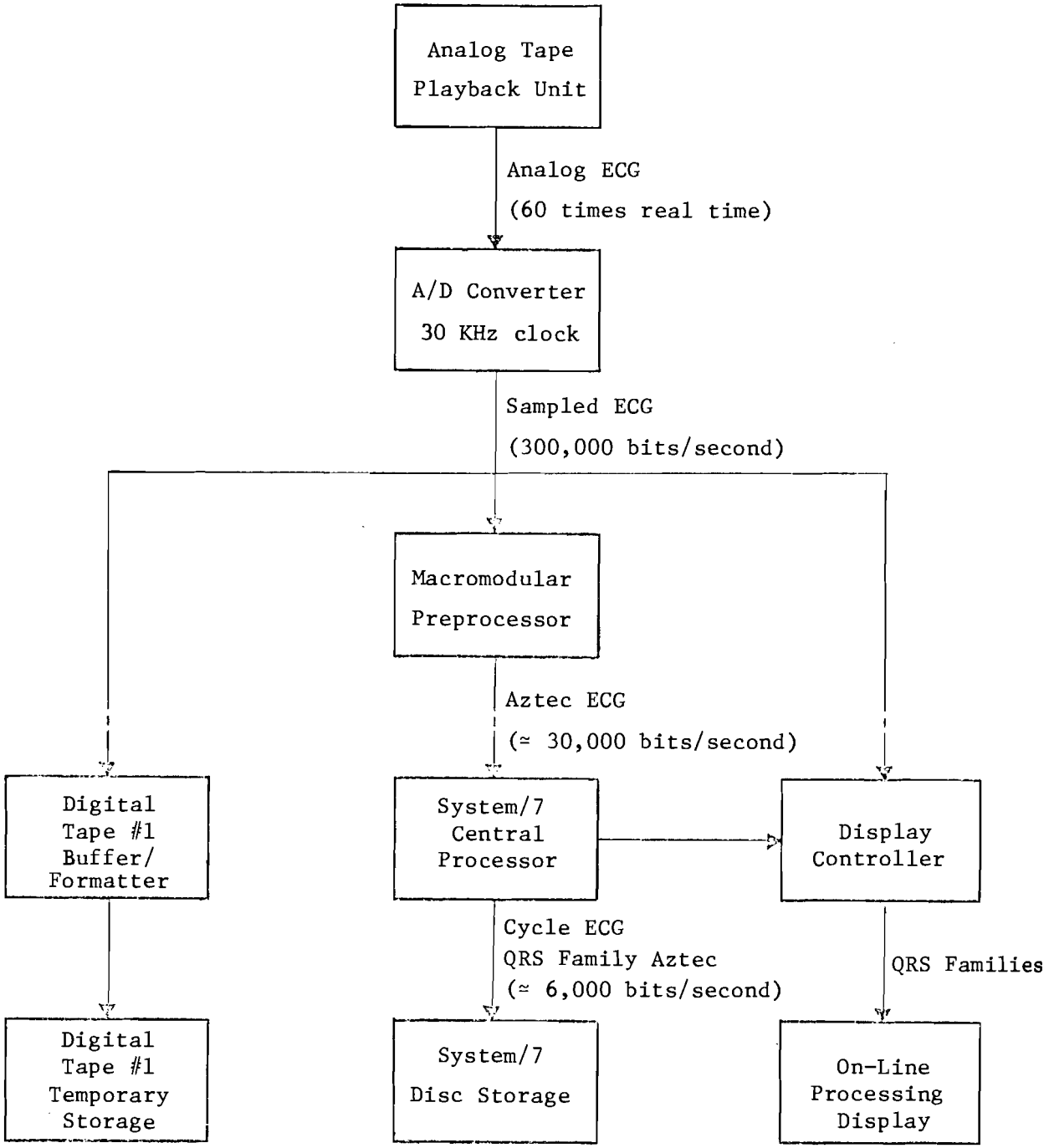

Figure 1. Preliminary diagram of the high speed ECG analysis system, data acquisition and initial data processing.

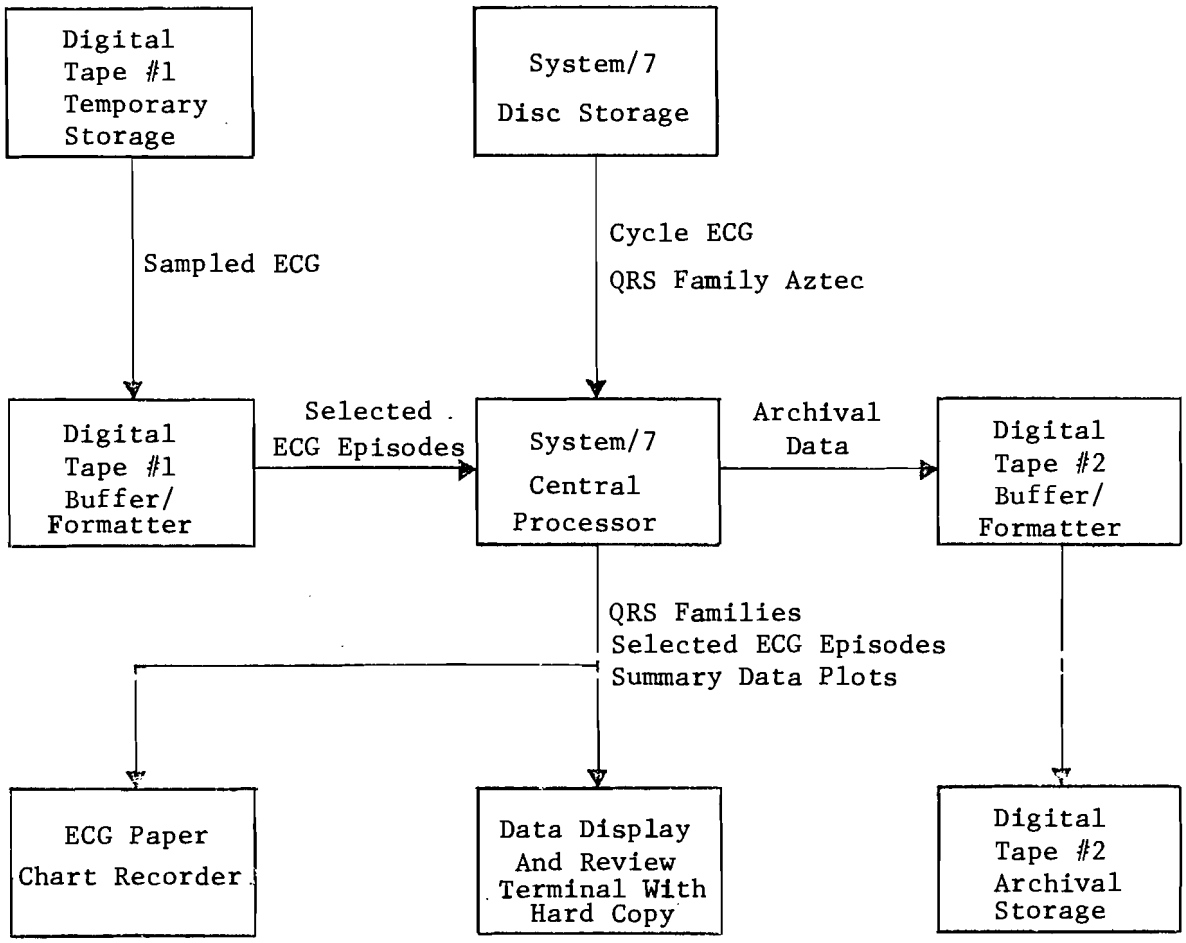

Figure 2. Preliminary diagram of the high speed ECG analysis system, data review and summary data generation.

B-6. Relationship of Ventricular Arrhythmias to Sudden Death--Modeling

Personnel: D. L. Snyder, BCL
K. W. Clark, BCL
G. C. Oliver, M.D., Medicine

Support: 71-2481
RR 00396

Work has begun on a statistical model for PVC occurrence. Many necessary programs have been written and tested to allow statistical analysis of PVC occurrence over long time periods. Data for this analysis has been obtained via the disc-oriented data storage system of Argus (see PR 7, B-3). Argus output, which is currently saved on disc for several hours, is periodically transferred to magnetic tape for more permanent storage. These tapes are processed using the LINC-8 for the extraction of statistical information on the incidence and occurrence patterns of PVCs. A variety of useful graphic displays have been developed, but the amount of data available for this type of analysis has been limited because the Argus patient computers, which can only process the original ECG data in real time, cannot often be diverted from their usual clinical duties.

Each PVC that occurs is labeled as one of five disjoint types according to the definitions that follow:

PVC Types (N=Non-PVC, V=PVC)

Type of PVC	Definition
Bigeminal	A PVC preceded by a Non-PVC beat preceded by a PVC preceded by a Non-PVC (i.e., the second PVC in the pattern NVNV)
Couplet	A PVC preceded by a PVC preceded by a Non-PVC beat (i.e., the second PVC in the pattern NVV)
Tachycardia	A PVC preceded by two PVCs (i.e., the third PVC in the pattern VVV)
Infrequent	A PVC preceded by one full minute of Non-PVC beats or also the first PVC in a record
Frequent	A PVC, not of any other type, preceded by a one minute interval containing at least one PVC.

A preliminary collection of LINC programs has been written to extract statistical information about PVCs and to present it graphically in a variety of ways. These programs and plots are described as follows:

Heart Rate, PVC Rate, and Data-Loss Rate averaged over one minute.

PVC Rate vs. Heart Rate. A point on the plot indicates the joint value of the PVC rate and heart rate averaged over a particular one minute period of time.

PVC Occurrences by Type. The height of a particular vertical line indicates the number of PVCs by type that have occurred in a one minute interval at the horizontal position of the line.

Scattergram for PVC Interarrival-Time Pairs. A point indicates the joint times between three successive PVCs regardless of type where the ordinate is the time between the first and second PVCs and the abscissa is the time between the second and third PVCs.

Interarrival-Time Histogram. Interarrival-time frequencies are plotted for all PVCs, regardless of type, of one record of data with time rounded to the nearest second. Similar histograms may be obtained for each type of PVC when sufficient occurrences exist.

PVC Record. PVC time indicates the time of occurrence of a PVC regardless of type. The type of PVC is indicated by the level of a piecewise constant function. A level change indicates that a PVC has occurred which differs from the preceding PVC.

PVC Record with Cumulative PVC Counts. A cumulative PVC count record superimposed on the PVC record indicates the total number of PVCs of all types that have occurred at any time. The slope of this function is a measure of the PVC rate.

PVC Summary by Type and Hour.

PVC Frequencies. Indicates the total number of PVCs by type that occur in a record.

PVC Pair Frequencies. Indicates the number of times in a record that specific PVC pairs occurred.

PVC Transition and Occurrence Relative Frequencies. The i-row, j-column entry $\hat{p}_{j|i}$ is an estimate of the probability that a PVC is of type j given that the preceding PVC was of type i.

Further work on the definitions of beat types is needed. For example, the second PVC in the stream ... N V V V V V ... is defined as a couplet PVC; the third and subsequent PVCs are labeled tachycardia PVCs. Clinically, the second PVC would not be considered part of a couplet event within a run of ventricular tachycardia. By our current definitions, a couplet PVC must precede a tachy PVC. This is clinically misleading. Therefore, some of our definitions must be reformulated to reflect clinical significance. Alternatively, the logic of the current programs could be modified to exclude conditional probabilities which arise solely as a result of the definitions.

Not all of the above methods of processing and presenting data will prove to be useful. Some other methods will certainly appear. The present list is useful as a start and will be modified as experience is gained with the output of the high-speed ECG analysis system.

B-7. A Commercial Version of Argus

Personnel: F. M. Nolle, BCL
J. R. Cox, Jr., BCL
T. Bellanca, Mennen-Greatbatch Electronics, Inc.
I. Teicher, Mennen-Greatbatch Electronics, Inc.

Support: Washington University

A commercial computer system has been developed by Mennen-Greatbatch Electronics, Inc.[1], for multiple-patient arrhythmia monitoring using the Argus algorithms (see PR 7, B-4). Extensive consultation has taken place in the last year on the numerous details of Argus' operation. The commercial version of Argus provides continuous monitoring of PVCs for any six patients selected from up to twenty patients. One such system will be installed shortly in the Barnes Hospital Coronary Care Unit (CCU) for testing and evaluation. A second system has been delivered to a community hospital as part of a newly constructed CCU, but is not yet being used clinically, awaiting the final testing of the system at Barnes. Plans for a prospective medical evaluation of the clinical import of the system at this community hospital are also underway.

[1] W. Greatbatch and T. Bellanca, "The ARGUS/SENTINEL Computer System for Arrhythmia Monitoring," submitted for publication to Medical and Biological Engineering.

B-8. The Cross-Correlation Coefficient and ECG Rhythm Analysis

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

Support: 71-2481
RR 00396

The cross-correlation coefficient has been used in other rhythm monitoring systems to compare the shape of a test QRS complex with that of a reference "stored normal" complex. However, there has been little available material concerning its behavior in actual practice.

The cross-correlation coefficient may be written as

$$\rho = \frac{\sum_{i=1}^{n} (x_i - m_x)(y_i - m_y)}{\sqrt{\sum_{i=1}^{n} (x_i - m_x)^2 \sum_{i=1}^{n} (y_i - m_y)^2}}$$

where the sets $\{x_i\}_{i=1}^{n}$ and $\{y_i\}_{i=1}^{n}$ are the components of the sampled data vectors for the stored normal wave, x, and for the test wave, y, respectively, and where

$$m_x = \frac{1}{n} \sum_{i=1}^{n} x_i$$

and

$$m_y = \frac{1}{n} \sum_{i=1}^{n} y_i$$

are their averages.

One property is that for any wave of the form $y = ax + b$ where $a > o$, the coefficient ρ has a value of unity. Thus, if the test wave in the electrocardiogram differs from the reference wave only in that there has been a change in amplitude or in the baseline, then the value of ρ for the test wave will be unity, the same as for the reference wave itself. In ECG rhythm monitoring systems, the value of ρ obtained for each test wave ($-1 \leq \rho \leq +1$) is used as a measure of the similarity of the wave to the stored normal wave.

In actual practice, the ECG has usually been sampled at 200 samples/s and the occurrence of QRS complexes has been detected by digital methods. A segment of sampled data (usually 300 ms in duration), extending backwards and forwards (usually in equal amounts) from a fiducial mark (usually the point of QRS detection), is used for the sampled data wave under test. The reference wave is obtained in the same manner, although an average of several such waves may also be used.

To study the cross-correlation coefficient, a computer program was developed to obtain a continuous plot of the coefficient as a function of time (the correlogram). ECG waveforms were digitized at 500 samples/s and normal reference QRS complexes centered in approximately 300 ms of context were manually selected. Point-by-point values 2 ms apart were computed for ρ as a reference waveform passed along its corresponding ECG signal. Figure 3 shows selected ECG waveforms and their corresponding correlograms. ECG records reconstructed from the 500 samples/s data are shown in the upper tracings, correlating normal reference waves are shown immediately below the

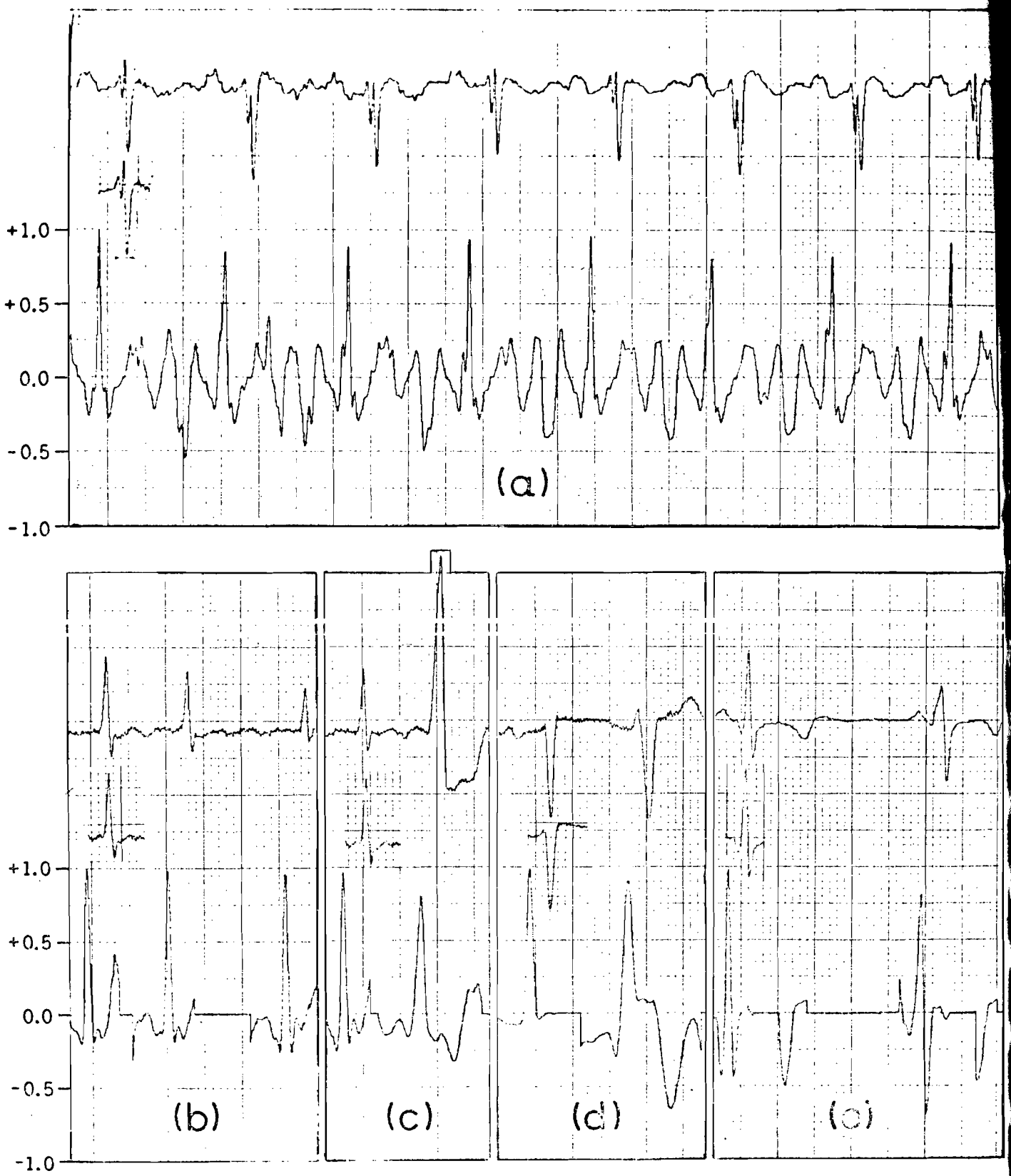

Figure 3. Plots of the Correlogram for Selected ECG Waveforms

first beat of the ECG, and the resulting correlogram is shown in the lower tracings. Note that the peak of the correlogram for the first beat is time aligned with the onset of the reference waveform rather than with its peak. The correlogram was clamped to zero when the standard deviation of the ECG fell considerably below the standard deviation of the reference, although this situation did not occur in the record of part (a). Vertical grid lines are 40 ms apart.

In Figure 3(a), beat-to-beat variations in the shape of a patient's normal QRS cause the peak values of the correlogram to vary between 1.0 and 0.8 at a cyclic rate commensurate with respiration. This example also demonstrates the striking steepness of the correlogram (width of 18-20 ms at a value of 0.5) for a QRS whose total duration is 80-100 ms. Record (b) illustrates its convenient auto-gain behavior for normal beats whose primary variation in shape seems to be a simple amplitude change (the rhythm is atrial fibrillation). However, another excerpt from the same record shows that the striking effect of a PVC pattern is greatly diminished in the correlogram (record (c)). Records (d) and (e) show other PVCs having high peak correlations with the normal references, reaching a value of 0.9 in record (d).

The peak values of the cross-correlation coefficient seen in Figure 3 represent the best possible values that could be obtained with a sampling rate of 500 samples/s. For "one-shot" calculation of the coefficient at each QRS, the exact location of the fiducial mark certainly has a great influence on the value obtained. A time shift of only 4 ms caused the coefficient to drop from a value of unity to 0.9 for one patient's QRS when correlated with itself. For sampling rates less than 500 samples/s the best possible values that can be obtained with optimal location of the fiducial mark will also be decreased. The combination of a considerably lower sampling rate and a less than optimal location of the fiducial mark would surely cause problems in some cases. Also, the record of Figure 3(a) indicates that multiple stored normal waves would be desirable in some cases.

The appeal of the cross-correlation coefficient for comparing ECG waveforms is due in large part to its apparent simplicity and ease of implementation. Since the technique does require a considerable amount of computer time for each calculation, refinements such as adding additional stored normal references, time shifting the test wave to find the peak of the coefficient, and increasing the sampling rate, would cause the computing time requirements to increase rapidly. In addition, the relative insensitivity of the coefficient to substantial differences in the durations of two waves such as those in Figure 3(d) suggests that the cross-correlation coefficient, as a single measure of the shape of QRS complexes, may not be sufficient for differentiating PVCs from normally conducted beats.

B-9. Digital Analysis of the Electroencephalogram, the Blood Pressure Wave, and the Electrocardiogram

Personnel: J. R. Cox, Jr., BCL
R. M. Arthur, Ph.D., Electrical Engineering
F. M. Nolle, BCL

Support: RR 00396
Washington University

A review article[1] covering pattern recognition techniques in the analysis of certain physiological signals has been completed. This review covers the electroencephalogram (EEG), the blood pressure wave, and the electrocardiogram (ECG), each producing patterns that the eye of the physician has empirically correlated with important aspects of health. Digital computer techniques for the recognition of these patterns are made particularly difficult by the realities of pattern context sensitivity, frequent signal artifact, real-time operation, finite storage limitations, and reasonable cost. Evaluations of these techniques are handicapped by the absence of absolute standards, the wide signal variability associated with pathologic states, and the sheer mechanics of comparison with human analysis.

Computer analysis of the EEG has been directed toward monitoring sleep stages and certain pathologic states, leaving the more difficult problem of diagnosis to the trained neurologist. Automatic pattern recognition of the blood pressure wave has been implemented with straightforward techniques for diagnostic use in the cardiac catheterization laboratory and for monitoring in the intensive care unit. Computer analysis of the ECG has been directed toward morphological and rhythm diagnosis, having great potential utility in clinical heart stations, and toward rhythm monitoring, a most practical application arising in coronary intensive care units.

Promising systems are emerging, but years of evaluation and adjustment will be necessary to meet the need for both accuracy and economy.

[1] J. R. Cox, Jr., F. M. Nolle, and R. M. Arthur, "Digital Analysis of the Electroencephalogram, the Blood Pressure Wave, and the Electrocardiogram," to be published in Proceedings of the IEEE.

B-10. Argus Hardware Additions and Modifications

Personnel: H. Dieter Ambos

Support: RR 00396
Barnes Hospital

Several improvements in the Argus hardware have been evaluated during the past year.

60 Hz Notch Filters. In order to allow Argus monitoring of patients whose ECGs exhibit consistent power line interference, a 60 Hz notch filter was installed preceding the analog buffer amplifiers in each patient computer (see PR 6, B-10). The filter response is down 3 db at 56 Hz and 64 Hz and down 27 db at 60 Hz. A toggle switch allows the filter to be switched in or out. Preliminary results show no significant increase in the number of false PVC episode alarms due to this addition.

ECG Signal Delay. A 30-second solid-state signal delay was installed for two beds at the acute area nurse station for testing and evaluation. The solid-state delay does not present the constant maintenance problems of the 45-second tape-loop cartridges now in use. The solid-state delay has been well received by both the nursing and technical staff who seem willing to forfeit the extra 15-seconds delay afforded by the tape loops.

New ECG Amplifier. An isolated ECG preamplifier was also evaluated in the Coronary Care Unit. It has a 10-megohm input imedance and therefore is less susceptible to 60 Hz interference caused by electrode impedance imbalance. During our evaluation a potential problem was uncovered and brought to the attention of the manufacturer, resulting in a slight design change.

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

Personnel: K. B. Larson, BCL
M. Blau, Ph.D., Roswell Park Memorial Institute
J. R. Cox, Jr., BCL
J. O. Eichling, Ph.D., Radiology
R. G. Evens, M.D., Radiology
M. Glos, Society of Nuclear Medicine
C. C. Harris, M.S., Duke University
E. J. Potchen, M.D. Radiology
R. H. Secker-Walker, M.D., Radiology
B. A. Siegel, M.D., Radiology
J. R. Wolff, M.S., Nuclear Chicago Corporation
K. L. Zierler, M.D., Johns Hopkins University
BCL Staff

Support: RR 00396
Washington University

The Society of Nuclear Medicine (New York) has agreed with BCL and with the Nuclear Medicine Division of the Radiology Department to publish, in permanent Proceedings form, the essential information developed and exchanged at the Workshop on Computer Processing of Dynamic Images from an Anger Scintillation Camera held at Washington University School of Medicine in January, 1971 (PR 7, C-1). Publication is scheduled for the early fall of 1972.

The contents of the book will consist of revised and updated versions of the notes prepared for the Workshop by members of the staffs of BCL and of the Division of Nuclear Medicine, as well as by invited authors at other universities and in industry. In addition, the Proceedings will contain summaries of the panel discussions devoted to various aspects of nuclear medicine which took place as an integral of the Workshop.

The Table of Contents from the Proceedings, summarized below, will give an indication of the range of topics treated.

Part 1. THE ANGER GAMMA-RAY CAMERA
1. Overview of Clinical Principles
2. The Anger Camera: Some Physical Considerations of its Design and Function
3. Gamma-Ray Camera Electronics

Part 2. PROCESSING OF DYNAMIC IMAGES WITH A COMPUTER
4. Interface Design Considerations
5. Design of Washington University Camera-Computer Interface
6. Computer Programming for Dynamic Image Processing

Part 3. MATHEMATICAL MODELS FOR INTERPRETING DYNAMIC TRACER DATA
7. Physical Principles of Tracer Kinetics

8. Why Tracer Dilution Curves Through a Vascular System Have the Shape They Do
9. Interpretation of a Clearance Curve in Terms of Compartmental Analysis
10. Statistical Analysis of Dynamic Tracer Data

Part 4. PANEL DISCUSSION SUMMARIES

11. Models for Dynamic Tracer Studies
12. The Gamma-Ray Camera for Brain Studies
13. The Gamma-Ray Camera for Lung Studies
14. The Gamma-Ray Camera for Kidney Studies
15. The Gamma-Ray Camera and Other Detectors for Multitracer Studies

Part 5. APPENDICES AND GLOSSARY

C-2. Measurement of Hemodynamic Parameters by Residue Detection in the Presence of Radiotracer Recirculation

Personnel: K. B. Larson, BCL
C. S. Coble, BCL
J. O. Eichling, Ph.D., Radiology
J. C. Metzger, M.A., Radiology
N. A. Mullani, BCL
P. E. Peters, M.D., Radiology
D. L. Snyder, BCL

Support: RR 00396
HE 13851

The use of residue detection[1,2] to measure hemodynamic quantities such as relative blood flow, relative blood volume, mean transit time, and transport-model parameters is complicated by radiotracer recirculation. The interpretation of such residue-detection curves has generally been based on mathematical models which either ignore recirculation, or attempt to correct for it by application of ad-hoc methods whose theoretical foundations are insecure and whose outcomes are therefore ambiguous. The classical methods of data analysis can fail when recirculation carries radiotracer back into the organ or region of interest and into adjacent perfused regions also within the detector field of view.

We have developed a mathematical model incoporating the physiological fact of tracer recirculation *ab initio*[3-7]. The model thereby accounts for added contributions to detector response due to recirculating tracer passing not only through the organ or region of interest, but also through adjacent perfused tissues. A further effect which the model recognizes is the possibility of arbitrary rates of tracer elimination from the circulation. Central to the model is the use of two injections of tracer, one at the arterial inflow and the other at the venous outflow of the particular vasculature of

interest. These give rise to a pair of residue curves. The two curves can be obtained simultaneously if radiotracers with differing decay-energy spectra are employed; otherwise, they must be obtained sequentially. 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 these are desired. These equations are natural generalizations of Zierler's "height/area" method [1,2] in that they are transport-model free. Nevertheless, if a particular transport-model is postulated, our method can yield its parameters. In particular, we give equations by means of which the parameters of one-and two-compartment models for a particular system of interest within the detector field may be derived from the data. No assumptions as to mechanisms of tracer transport, compartmental or otherwise, need be made for other systems inside or outside the detector field.

Our model has been employed successfully for measuring relative blood flow and relative blood volume in a number of clinical and laboratory applications within the Radiology Department at Washington University Medical School. The use of our technique to measure relative cerebral blood volume (CBV) in rhesus monkeys has been shown to give values in agreement with those obtained by the X-ray fluorescence technique (see C-5). Agreement is also obtained between the two methods in measurements of the effect of arterial carbon dioxide tension (P_{CO_2}) on cerebral blood volume. In contrast, the conventional Stewart-Hamilton exponential-extrapolation method of correcting for tracer recirculation leads to values of CBV too small by about a factor of two in comparison with those obtained by the X-ray method. Moreover, the Stewart-Hamilton approach predicts values of CBV which show no correlation with arterial P_{CO_2}, contradicting the findings obtained with the X-ray method.

Measurements of cerebral blood volume in human patients has also been made using our dual-injection residue-detection method, but it is still too early to assess its value for routine clinical use.

Myocardial blood-flow studies[8] using *in vivo* perfused dog heart preparations have illustrated the validity of our theory. The radioactive tracers oxygen-15 labeled water and xenon-133 were used as the test indicators. In these preparations, the animal's own blood was pumped at a known rate through a catheter tied into the left common coronary artery. In this manner, flow values calculated from the isotope technique could be compared with the pump flow. The arterial bolus injections were made into the left common coronary artery via the perfusion line using an automatic injector, and the venous injections were made via a catheter in the right atrium at the coronary sinus. The paired injections were identical in volume, rate, and duration. The method using the paired arterial-venous injections for recirculation correction resulted in an observed average overestimate of pump flow of 3.1%, (S.E. = 2.9%, n = 7), which was shown not to be statistically different from pump flow, at the 5% significance level[8]. Attempts to correct for recirculation of xenon-133 were unsuccessful, as the paired curves could not be normalized to an equilibrium value.

In addition to the above applications of our method for interpreting actual physiological data, we propose to employ it with physical flow models which we intend to construct from appropriate combinations of tubing, pumps, flow meters, mixing vessels, and radioactivity detectors. These elements are to be interconnected in configurations which will enable the potential of our mathematical model to be studied under well-defined conditions. Among the issues which such a study can be hoped to elucidate are the effects of noisy and incomplete data and of spatial and temporal non-uniformities in detection efficiencies.

(1) K. L. Zierler, "Equations for Measuring Blood Flow by External Monitoring of Radioisotopes", Circ. Res., 16, 309-321, 1965.

(2) K. L. Zierler, "The Cardiovascular System", in Compartments, Pools, and Spaces in Medical Physiology, P.-E. E. Bergner and C. C. Lushbaugh, editors, U. S. Atomic Energy Commission, 265-281, 1967.

(3) K. B. Larson and D. L. Snyder, "Measurement of Relative Blood Flow, Transit-Time Distributions, and Transport-Model Parameters by Residue Detection when Radiotracer Recirculates", J. Theor. Biol., 1972, in press.

(4) K. B. Larson, D. L. Snyder, and J. O. Eichling, "Measurement of Blood Flow by External Monitoring of Radiotracers when Recirculation Interferes", presented at the 24th Annual Conference on Engineering in Medicine and Biology, Las Vegas, Nevada, November 4, 1971.

(5) K. B. Larson, D. L. Snyder, and J. C. Metzger, "Measurement of Blood Flow and Determination of Transport-Model Parameters by External Monitoring of Radiotracers When Recirculation Interferes", presented at the Winter Meeting of the American Physical Society, Cambridge, Massachusetts, December 27, 1972.

(6) K. B. Larson and D. L. Snyder, "A Mathematical Model for Measuring Blood Flow by Residue Detection When Radiotracer Recirculation Interferes", Proceedings of the National Conference on Research Animals in Medicine, National Heart and Lung Institute, U. S. Government Printing Office, 1972, in press; presented at the Conference, Washington, D. C., January 29, 1972.

(7) K. B. Larson and D. L. Snyder, "Measurement of Blood Flow by Residue Detection When Recirculation of Tracer Interferes", invited seminar presented at the Department of Physiology, St. Louis University School of Medicine, St. Louis, Missouri, March 2, 1972.

(8) J. C. Metzger, "Myocardial Blood Flow and Oxygen Consumption Using $H_2{}^{15}O$ and ^{15}O-Hemoglobin," Ph.D. Thesis, Washington University School of Medicine, August, 1972.

C-3. The Interpretation of Mean Transit Time Measurements for Multiphase Tissue Systems

Personnel: K. B. Larson, BCL
G. W. Roberts, Sc.D., Chemical Engineering
E. E. Spaeth, Ph.D., Chemical Engineering

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We have developed a model-independent proof of the central-volume principle of indicator-dilution theory[1,2]. Our derivation emphasizes the transport processes which occur within the system, and the physical constraints which the system must satisfy for valid application of the principle. These constraints are: (a) the fluid flowing into the system must be equivalently-labeled; and (b) the system under study must be part of a larger system which has no diffusive inlets or outlets. The derivation shows that the definition of the volume of distribution and the choice of appropriate partition coeffecients are independent of any assumptions concerning tracer equilibrium in the interior of the phases. A new and less restrictive definition of equivalent labeling also follows from the derivation.

We have derived a relationship between the mean transit times measured by residue detection and that measured by outflow detection, and shown that if diffusion of tracer across the system boundaries is significant compared with convective transport, then these two transit times differ.

Finally, we have established conditions under which valid measurements of regional blood flow and regional blood volume can be inferred from residue-detection data. We find that regional residue-detection measurements may be potentially useful in assessing variations in structure throughout a larger region. Our analysis shows that when tracer enters the detector field by diffusion, as well as by convection, the use of the "height/area" method[2] for calculating regional perfusion can yield erroneous values. The results summarized here have been submitted for publication[3].

(1) J. L. Stephenson, "Theory of Measurement of Blood Flow by Dye Dilution Technique," IRE Trans. Med. Electronics, PGME-12, 82-88, 1958.

(2) K. L. Zierler, "Equations for Measuring Blood Flow by External Monitoring of Radioisotopes", Circ. Res., 16, 309-321, 1965.

(3) G. W. Roberts, K. B. Larson, and E. E. Spaeth, "The Interpretation of Mean Transit Time Measurements for Multiphase Tissue Systems," submitted for review and possible publication to J. Theor. Biol., 1972.

C-4. A Mathematical Model for Design and Analysis of Experiments to Measure Cerebral Utilization Rate by External Monitoring of Radioglucose

Personnel: K. B. Larson, BCL
R. L. Grubb, Jr., M.D., Radiology
J. Hecht, B.A., Radiology
M. E. Phelps, Ph.D., Radiology
M. E. Raichle, M.D., Radiology
M. M. Ter-Pogossian, Ph.D., Radiology
M. J. Welch, Ph.D., Radiology

Support: RR 00396
HL 13851
Washington University

We have developed a mathematical model to aid in the interpretation of laboratory measurements intended to measure cerebral glucose utilization rates in the rhesus monkey. The method employs an intravenous injection of carbon-11 labeled glucose; cyclotron-produced radiocarbon is used to label glucose by a photosynthetic technique. Radioactivity is monitored continuously after injection of radioglucose by means of two scintillation detectors. One detector measures the total radioactivity in the head, while the second provides a measure of radioglucose in arterial blood. The ultimate objective is to develop a non-invasive, atraumatic procedure applicable in a clinical setting for measuring regional glucose uptake in humans.

The mathematical model relates the detector responses to the glucose utilization rate and allows a quantity proportional to the latter to be obtained with only about two to three minutes of counting data. By assuming zero egress of carbon-11 labeled metabolites of glucose from brain tissue in the first few minutes after injection[1], we obtain the rate of brain-tissue radioglucose uptake as the difference between total head radioactivity accumulation rate and cerebral vasculature accumulation rate. Differences in counting geometries of the two detectors are taken into account by means of responses to a second injection of the subject's own red cells labelled with oxygen-15-labeled carbon monoxide.

We have incorporated the concept of mediated transport of glucose[2,3] across the blood-brain barrier[4] into our model in order to account for the observed decrease in the rate of radioglucose uptake in tissue with time. Relative glucose utilizations predicted by our model have been found to correlate well with those determined by the Fick principle using measured arterial and venous blood glucose concentrations and blood flows.

[1] W. Sacks, "Cerebral Metabolism of Doubly-Labeled Glucose in Humans in Vivo," J. Appl. Physiol., 26, 117-130, 1965.

(2)W. F. Widdas, "Facilitated Transfer of Hexoses Across the Human Erytheocyte Membrane," J. Physiol., 125, 163-180, 1954.

(3)P. G. LeFevre and G. F. McGinnis, "Tracer Exchange vs. Net Uptake of Glucose Through Human Red Cell Surface: New Evidence for Carrier-Mediated Diffusion," J. Gen. Physiol., 44, 87-103, 1960.

(4)P. M. Buschiazzo, E. B. Terrell, and D. M. Regen, "Sugar Transport Across the Blood-Brain Barrier," Am. J. Physiol., 119, 1505-1513, 1970.

C-5. Statistical Analysis of Data on Relative Cerebral Blood Volume Obtained by Means of Stimulated X-Ray Fluorescence

Personnel: K. B. Larson, BCL
R. L. Grubb, M.D., Radiology
M. E. Phelps, Ph.D., Radiology
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 00396
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HL 13851
Washington University

An *in vivo* X-ray fluorescence technique described elsewhere(1) was employed to investigate the effect of CO_2 tension (P_{CO_2}) in arterial blood on relative cerebral blood volume (CBV) in the rhesus monkey. Varying values of arterial P_{CO_2} were induced in seven experimental animals by means of controlled CO_2 flows to a respirometer, and the corresponding values of CBV were determined(2).

Statistical analyses of the data were performed in order to test for linear trends between CBV and P_{CO_2} and in order to determine whether additional parameters might be influencing the observations. These tests were based on the method of analysis of variance in conjunction with weighted least-squares linear regression. The requisite computations were made using an IBM 360 Model 50 and FORTRAN programs written for the purpose. Linear trends of increasing CBV vs. P_{CO_2} were demonstrated at a significance level of 0.05 for each of the seven animals, and at a significance level of 0.005 for an overall linear regression involving all the data(2).

An additional analysis of variance for the linear regression coefficients revealed differences in slope among the seven animals at a significance level of 0.01. This result was interpreted as indicating that one or more additional uncontrolled parameters were influencing the observed values of CBV. Subsequent experimentation revealed that the parameter in question was arterial blood pressure. It was therefore recognized that in future measurements of

CBV, both arterial blood pressure and arterial P_{CO_2} must be treated as independent variables, and that both quantities must be controlled and monitored simultaneously.

(1) M. M. Ter-Pogossian, M. E. Phelps, and M. Lassen, "In Vivo Measure of Regional Cerebral Blood Flow and Blood Volume by Means of Stimulated X-Ray Fluorescence", in The Role of Semiconductor Detectors in the Future of Nuclear Medicine, P. B. Hoffer, R. N. Beck, and A. Gottschalk, eds., Society of Nuclear Medicine, New York, New York, 1971.

(2) M. E. Phelps, R. L. Grubb, and M. M. Ter-Pogossian, "Correlation Between Arterial Carbon Dioxide Tension and Regional Cerebral Blood Volume by X-Ray Fluorescence", submitted for review and possible publication in J. Appl. Physiol., 1972.

C-6. Parameter Estimation for Radioisotope Tracer Data

Personnel: D. L. Snyder, BCL
P. Fishman, M.S., Applied Mathematics and Computer Science
N. A. Mullani, BCL
M. J. Phelps, Ph.D., Radiology

Support: RR 00396
HL 13851

The objective of this continuing study is to develop efficient computer techniques for processing radioisotope tracer data from the gamma camera or an array of detectors when the interarrival times between detected events are collected (see PR 7, C-19). The interface to the LINC computer previously described for collecting these times (PR 7, C-21) has been improved to eliminate data losses experienced in the original design due to random synchronization failures. Interarrival times have been collected by monitoring the natural radiation of oxygen-15, carbon-11, and mixtures of oxygen-15 and carbon-11; this data is described in Table I and will be used as a standard for testing parameter estimation algorithms. The data of Run Number 10 has been used in a preliminary study of maximum likelihood parameter estimation techniques on the LINC computer.

Our model and results described in (PR 6, C-13) and (PR 7, C-21) have been extended to include spatial as well as temporal effects. This extended model is important in the development of parameter estimation techniques that use the signals from all elements in a probe array simultaneously rather than individually as is the current practice.

Run Number	Isotope	Start Count Rate (c/s)	End Count Rate (c/s)
1	O-15	2000	600
2	O-15	1200	200
3	O-15	4000	400
4	C-11	200	55
5	O-15 and C-11	620	100
6	O-15	4000	400
7	O-15	4000	400
8	O-15	4000	400
9	O-15	3000	160
10	O-15	3000	120
11	O-15	3000	150

TABLE I

The approximate estimates described in (PR 7, C-22) have been published[1,2].

[1]D. L. Snyder, "Filtering and Detection for Doubly-Stochastic Poisson Processes," IEEE Trans. on Information Theory, IT-18, 91-102, January, 1972

[2]D. L. Snyder, "An Approximate Nonlinear Filtering Theory for Processing Data Obtained in Nuclear Medicine," Proc. 1972 IEEE International Symp. on Information Theory, Asilomar Conf. Grounds, Pacific Grove, Calif., January, 1972.

C-7. A Model for Flow in Vasculatures

Personnel: S. C. Huang, BCL
J. R. Cox, Jr., BCL
S. Lang, Ph.D., Physiology & Biophysics
D. L. Snyder, BCL
L. J. Thomas, M.D., BCL, Physiology and Biophysics, and Anesthesiolog

Support: RR 00396
Washington University

The goal is to relate transit time distributions of intravascular tracers to the physiological structure of vascular beds. Due to the complexity of the structure of a vascular bed, the analytic determination of transit time distributions is not easy. Therefore, we construct a reasonable model for flow in

vasculature according to known information, and we find the transit time from the model.

The present model for flow in vasculatures is based on the following assumptions:

1. Blood is mostly stored in small venous vessels.

2. Branch lengths of different branching levels are statistically independent for small venous vessels (PR 7, C-26).

3. The flow in small venous vessels can be approximated as plug flow.

4. At every branching point of small venous vessels, mean velocities in the two daughter branches are the same, and, for the same level, the mean velocity in daughter vessels divided by that in the parent is deterministic.

These assumptions are supported either by our own observations or by findings of others.

Following the assumptions, transit time through a vascular bed can be represented by the sum of two terms. One is a deterministic value (t_d) and the other is a ratio of two independent random variables (L/v_m). The variable L is related to the structures of small venous vessels and has a Gaussian distribution. The variables t_d and v_m are related to flow in large venous vessels, and the distribution of v_m can be taken as a beta distribution.

According to this model, the skewness of transit time distributions is primarily due to the velocity distribution of tracer particles in a vasculature. The transit time distribution from the present model has been used to fit many experimental curves of different organs from the literature with good results.

Despite the differences in flow and venous pressure conditions, curves from the same kind of organ seem to have consistent values of relative deviation (standard deviation/mean) for the distributions of L, while they are quite different from one kind of organ to another. This observation is consistent with the model because, in the model, L is related only to the structure of small venous vessels, which is not altered significantly by changes in flow and venous pressure.

Further physiological interpretations of parameters in the model are being sought and animal experiments are being planned to test the model.

C-8. Specification of a New Computer System for Radiation Physics

Personnel: N. A. Mullani, BCL
C. S. Coble, BCL
J. R. Cox, Jr., BCL
M. E. Phelps, Ph.D., Radiology
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 00396
HL 13851
Washington University

For the past two years, the Radiation Physics Department of the Washington University School of Medicine has very effectively used a Classic LINC for data collection, storage and processing from scintillation detectors. However, due to an expansion of activities and the addition of a 26 probe system (see C-9) a larger computer system was required for the department.

The requirements of the new system are: (1) at least two experiments to be monitored concurrently; (2) fast floating-point arithmetic for data analysis; (3) fast graphical output; (4) a fast-access mass-storage device; and (5) a problem oriented programming language such as FORTRAN. The search for the new computer was limited to those having 16-bit words with 8K or more of memory. A dual processor system was purchased to satisfy the above requirements and financial constraints. The system includes the following components:

INTERDATA 70 with 8K of memory;

INTERDATA 80 with 8K of memory;

VERSATEC 1100 A, 600 lines-per minute-graphical line printer; and

DIABLO 33, dual moveable-head discs.

C-9. Design and Construction of a 26-Probe System for Isotope Detection

Personnel: M. E. Phelps, Ph.D., Radiology
N. A. Mullani, BCL

Support: RR 00396
HL 13851

A twenty-six-probe system, which consists of a lead head shield, 2"-by-2" NaI(Tl) detectors with focusing collimators, preamps, high-voltage supplies, amplifiers and single-channel analyzers, has been constructed. A computer system (see C-8) is presently being interfaced to the probes and a program library is being developed for the data acquisition and processing.

This system will be used for regional cerebral blood flow, blood volume, oxygen utilization and glucose utilization studies in human subjects. Most of the protocol for these studies has been developed with the six-probe system and the LINC computer that is presently used in the Radiation Physics laboratory. The 26-probe system will provide a marked improvement in the regionality of these studies. However, the size of this system necessitates an automatic-calibration and data-analysis scheme that is presently being developed.

C-10. Color Video Display of Gamma-Camera Data

Personnel: N. A. Mullani, BCL
D. J. Bax, BCL

Support: RR 00396

A color video display system is being designed to display a 64-by-64 element array in the form of a color picture representing data collected from a gamma camera. The system is planned to display up to 64 different colors or shades of grey and will use a commercially-available color television receiver with a built in buffer memory for one frame to produce flicker-free displays.

C-11. Ventilation-Perfusion Studies Using the Gamma Camera

Personnel: R. H. Secker-Walker, M.D., Radiology
J. M. Baker, BCL
R. L. Hill, BCL
J. Markham, BCL
E. J. Potchen, M.D., Radiology

Support: RR 00396
AT(11-1)-1653
Washington University

More than 200 subjects have now been examined by the method described previously (PR 7, C-5), including 22 healthy volunteers, 29 patients with pulmonary embolism, 57 patients with chronic obstructive lung disease, 15 patients with both conditions, 20 patients with carcinoma of the bronchus and 2 with emphysematous bullae for surgical resection. A number of patients have been examined twice, and the remaining subjects suffered from a variety of pulmonary diseases.

In the normal volunteers the fractional exchange of air per breath increased from apex to base in the expected fashion. The left lung was ventilated slightly more efficiently than the right, expecially at the left

base. No lateral gradient was observed in either lung. A good correlation ($r > 0.8$) was found between the fractional exchange of air per breath and tidal volume. The exchanged volume (determined from the product of the lung volume and the fractional exchange of air per breath) differed from the tidal volume by 200-250 ml when the tidal volume was 1000 ml. This difference represents anatomic dead space and physiologic dead space.

The patients with pulmonary embolism showed a normal distribution of ventilation, while those with chronic obstructive lung disease showed a wide range of values in keeping with the disturbance of ventilation that is known to occur in this condition. The information obtained in the patients with carcinoma of the lung has been used to influence the decisions in surgical management on occasion.

The tissue background correction, incorporated into the calculation, allows the washout curves to be used and this enables a more accurate assessment of ventilation to be made from this part of the study than could be done otherwise.

At the present, the relative distribution of perfusion, the relative distribution of ventilation, and the efficiency of ventilation are determined for three regions in each lung. Grey-scale functional images are prepared to give an overall impression of these relationships.

A new program, which is almost ready, will provide a measure of the ventilation-perfusion ratios, by combining the fractional exchange of air with the perfusion lung scans.

In addition, preliminary experiments have been performed on the measurement of ventilation by transmission, with the wedge spirometer interfaced to the computer, and a systematic evaluation of this method will take place shortly.

A series of papers[1-3] describe these investigations.

(1) R. H. Secker-Walker and R. G. Evens, "The Clinical Application of Computers in Ventilation-Perfusion Studies," in Progress in Nuclear Medicine, in press.

(2) R. H. Secker-Walker, R. Hill, J. Markham, and E. J. Potchen, "Clinical Applications of Regional Ventilation Measured with a Scintillation Camera and a Small Digital Computer," J. of Nuclear Medicine, 13, 466, June, 1972.

(3) R. H. Secker-Walker, R. Hill, J. Markham, J. Baker, and E. J. Potchen, "The Measurement of Ventilation in Man: A New Method of Quantification," Investigative Radiology, in press.

C-12. Cardiac Ejection Fraction

Personnel: R. H. Secker-Walker, M.D., Radiology
R. L. Hill, BCL
J. A. Parker, M.D., Radiology
E. J. Potchen, M.D., Radiology
L. Resnick, M.D. Radiology

Support: RR 00396
AT(11-1)-1653
GM 01747
Washington University

The method described previously (PR 7, C-7) has now been used to measure left ventricular ejection fraction in 16 subjects and also in 9 dogs.

Technetium-99m-labeled human-serum albumin is used as the tracer. After a bolus injection, one-second images are collected for 100 seconds as the the tracer passes through the heart. The borders of the left ventricle can be determined from this part of the study.

Images of end-diastole and end-systole are collected for 45-ms intervals during each cardiac cycle using the R-wave of the electrocardiogram to define end-diastole, and the last 45 ms of the T-wave to define end-systole.

In three normal subjects the left ventricular ejection fraction varied between 50-83%, while in the patients it varied between 22-84%. In 10 patients a comparison with the ejection fraction from left ventricular angiography was made, and a good correlation ($r > 0.8$) was found.

In the experiments on the dogs the effect of a variety of drugs on cardiac function was studied, including isoproteronol, lidocaine, propranolol and calcium chloride. The expected results were obtained with an increased ejection fraction after isoproteronol, a decrease with lidocaine and propranolol and some restoration towards normal with calcium chloride.

In both patients and dogs the actual figures for the ejection fraction vary, depending on just what region is chosen as the left ventricle. Fairly constant results can be obtained by carefully choosing a region with the help of three displays: (1) the end-diastole image, (2) the end-diastole and end-systole images shown alternately, imitating the pumping action of the heart, and (3) the end-diastole minus the end-systole image.

Work to date has been described[1-2] and further work is in progress on modifications of the algorithm used to measure the tissue background.

[1] J. A. Parker, R. H. Secker-Walker, R. Hill, B. A. Siegel, and E. J. Potchen, "A New Technique for the Calculation of Left Ventricular Ejection Fraction," J. of Nuclear Medicine, in press.

(2) J. A. Parker, R. H. Secker-Walker, R. Hill, E. J. Potchen, B. Siegel, and L. Resnick, "The Measurement of Left Ventricular Ejection Fraction Using a Scintillation Camera and a Small Digital Computer," J. of Nuclear Medicine, 13, 459, 1972.

C-13. Computer-Assisted Renography

Personnel: R. H. Secker-Walker, M.D., Radiology

Support: RR 00396
AT(11-1)-1653
Washington University

Static images of the kidneys obtained two hours after the intravenous injection of mercury-197-labeled chlormerodrin, and sequential 20-second images of the changing distribution of iodine-131-labeled Hippuran are recorded digitally on magnetic tape.

The static image is used to outline the region of the kidneys for the renogram, and also to determine relative function from the amount of activity in each kidney. A tissue background region is outlined between each kidney, so that the large fraction of activity contributed from the overlying tissues can be accounted for.

Figures for the relative function of each kidney are also obtained from the area beneath the renogram curves before the first peak is reached.

The examination has been used almost exclusively in the preoperative assessment of patients with obstructive uropathy, but occasionally in patients with hypertension and also in following the function of a transplanted kidney. Publication of these investigations has appeared(1).

(1) R. H. Secker-Walker, E. P. Shepherd, and K. J. Cassell, "Clinical Applications of Computer Assisted Renography," J. of Nuclear Medicine, 13, 235-248, April, 1972.

C-14. Reducing the Motion Artifact in Clinical Studies of the Liver

Personnel: P. H. Weiss, M.D., Radiology
J. M. Baker, BCL
E. J. Potchen, M.D., Radiology
R. H. Secker-Walker, M.D., Radiology

Support: RR 00396
GM 01747

We have begun to study this problem with a system similar to that of Oppenheim[1]. Data is collected from the scintillation camera and fed through dual analog-to-digital converters using a 32-by-32 matrix on the PDP-12 computer. The program allows variation in frame length and in the area used for motion correction. Each frame is summed and the row where the median count occurred determined. This row is assumed to locate the center of mass of the liver. The image is then transferred to another location in memory with all the median rows aligned. These operations are performed before and during the collection of the next data frame; thus the corrected image is available immediately at the end of the collection. The uncorrected image is also stored and is available at the end of the collection. In addition, the position of the median row is plotted during the collection and is displayed on the oscilloscope. This documents respiratory excursion of the image.

Our studies in patients have shown excursions averaging 0.7 to 1.0 cm in the anterior projection during quiet respiration. During deep breathing, this increases to 2 to 3 cm, which is consistent with maximal inspiratory and expiratory differences measured radiographically[2]. Significant differences have been found between erect and recumbent positions with the upright position producing the least motion.

The major limitation on the system at present is the use of the 32-by-32 matrix. This matrix size significantly degrades camera resolution with the parallel hole collimator, and this limitation becomes even more critical in view of the small excursion of the liver during respiration.

We plan to use a finer matrix when more memory becomes available, and to use objective criteria to assess the effects of motion on the degradation of the image. Results to date have been reported[3].

(1) B. E. Oppenheim, "A Method Using a Digital Computer for Reducing Respiratory Artifact on Liver Scans Made with a Camera," J. of Nuclear Medicine, 12, 625-628, 1971.

(2) R.G. Fraser and J. A. Pare, Diagnosis of Diseases of the Chest, W. B. Saunders and Co., Philadelphia, 1970.

(3) P. H. Weiss, J. Baker, and E. J. Potchen, "Assessment of Hepatic Respiratory Excursion," J. of Nuclear Medicine, in press.

C-15. Gastric Emptying

Personnel: B. A. Siegel, M.D., Radiology
J. M. Baker, BCL
R. L. Hill, BCL

Support: RR 00396
GM 01747
Washington University

The *in vivo* study of gastric emptying via the gamma-camera-PDP-12 system as previously described (PR 7, C-9) has continued. During the past year, 24 patients have been referred for study for a variety of disorders including: 1) evaluation of gastric obstruction, 2) evaluation of effects of drugs on gastric emptying and reactive hypoglycemia, 3) evaluation of gastric emptying and disordered carbohydrate metabolism in chronic renal disease before and after initiation of hemodialysis, 4) evaluation of gastric involvement in diabetic neuropathy; and 5) evaluation of results of vagectomy for duodenal ulcer. The numbers of patients studied in each group is too small to reach conclusions at present, but these projects will be continued.

C-16. A Multiprobe System for the PDP-12

Personnel: J. M. Baker, BCL
R. L. Hill, BCL

Support: RR 00396

A multiprobe interface has been designed and built for the PDP-12. This interface is capable of counting detected nuclear events from one to eight individual scintillation detectors. The interface is comprised of two printed circuit boards, one of which is a module containing eight 12-bit binary counters; the other contains sufficient control logic to handle up to eight counter modules for an ultimate capability of 64 detectors. The system was designed in a modular fashion to allow expansion in groups of eight detectors simply by duplicating the counter module.

The contents of from one to sixty-four counters are transferred directly to computer memory and cleared by executing a single instruction in the PDP-12. A three-cycle data break, a direct memory access feature of the PDP-12, is used to effect the transfer and requires 4.8 microseconds to transfer each counter. In the event of overflow of any one of the 12-bit counters, a program interrupt is caused and this condition can be verified and handled within the interrupt service routine.

A program has been written to collect sequential samples from detection systems containing from one to eight probes. The time interval of each sample can be entered and remains fixed throughout the study. A triple-precision (36-bit) buffer area is reserved for each probe and each 12-bit counter word can be added to its buffer after transfer. Sequentially-collected 36-bit data words can then be stored on LINC tape. Another feature of the program allows teletype printing of the triple-precision words after conversion to decimal.

C-17. Intensity Modulation for the PDP-12 Display

Personnel: J. D. Ferrario, B.S., Radiology
J. M. Baker, BCL
R. L. Hill, BCL

Support: RR 00396
AT(11-1)-1653

In order to reduce the time required to generate displays of the spatial distribution of radioisotope data collected with the gamma camera-PDP-12 system, we have implemented a program-controlled intensity modulation scheme for the display oscilloscope of the PDP-12. This scheme involves a digital-to-analog conversion of a six-bit word transferred from the accumulator of the PDP-12. The analog signal is added to the intensity control voltage resulting in a smoothly-varying 64-level intensity modulation. The modification results in a time savings ranging from a factor of ten to twenty when generating displays of the spatial distribution of a radioisotope.

C-18. Techniques Useful for the Compression of Data from Scintillation Cameras

Personnel: R. L. Hill, BCL

Support: RR 00396

Data are collected from the gamma-camera in the form of arrays of integers, with each entry of an array representing the number of nuclear events detected in a small area of the gamma camera detector and the address of each entry representing its position on the face of the camera. We have used 32-by-32 arrays of 1024 entries each for dynamic studies in nuclear medicine. The time required to transfer each array to magnetic tape limits the minimum array-integration interval to 0.4 second. The gamma camera, however, reaches an upper limit of usefulness at about 20,000 counts per second and

a 32-by-32 array integrated over 0.1 second would have an average of only two counts per element at that maximum counting rate. For various spatial distributions of radioactivity, this results in an entropy or average information per element of only two or three bits per 12-bit word. The use of data-compression techniques is clearly indicated.

A composite sample distribution of array elements was formed from a mixture of sixteen routine brain views, lateral, anterior, and posterior. A total of 256, 32-by-32 arrays, each averaging two counts per element, were collected and the resultant distribution had an entropy of 2.65 bits per word. A Huffman code[1] was constructed for the composite distribution which had an average code word length of 2.7 bits. The Huffman code construction technique is a systematic way of constructing a variable-length code where the shortest code words are assigned to the source words having the highest probability of occurrence. The result is a uniquely decodable code of minimum average length.

To test the feasibility of the code, it was applied to another twenty routine brain views, the object being to always code a 32-by-32 array into less than 256, 12-bit words (four-to-one compression) and to carry out the processing required by the coding algorithm in less than 85 ms. Figures 1 and 2 show the results of the study[2]. This four-to-one data compression results in a reduction of the minimum array integration time from 0.4 to 0.1 second.

[1] N. Abramson, Information Theory and Coding, McGraw-Hill Publishing Co., 1963, p 77.

[2] R. L. Hill, "Block Coding for Data Compression in Nuclear Medicine," Proc. 1972 IEEE International Symposium on Information Theory, Asilomar Conf. Grounds, Pacific Grove, Calif., January, 1972.

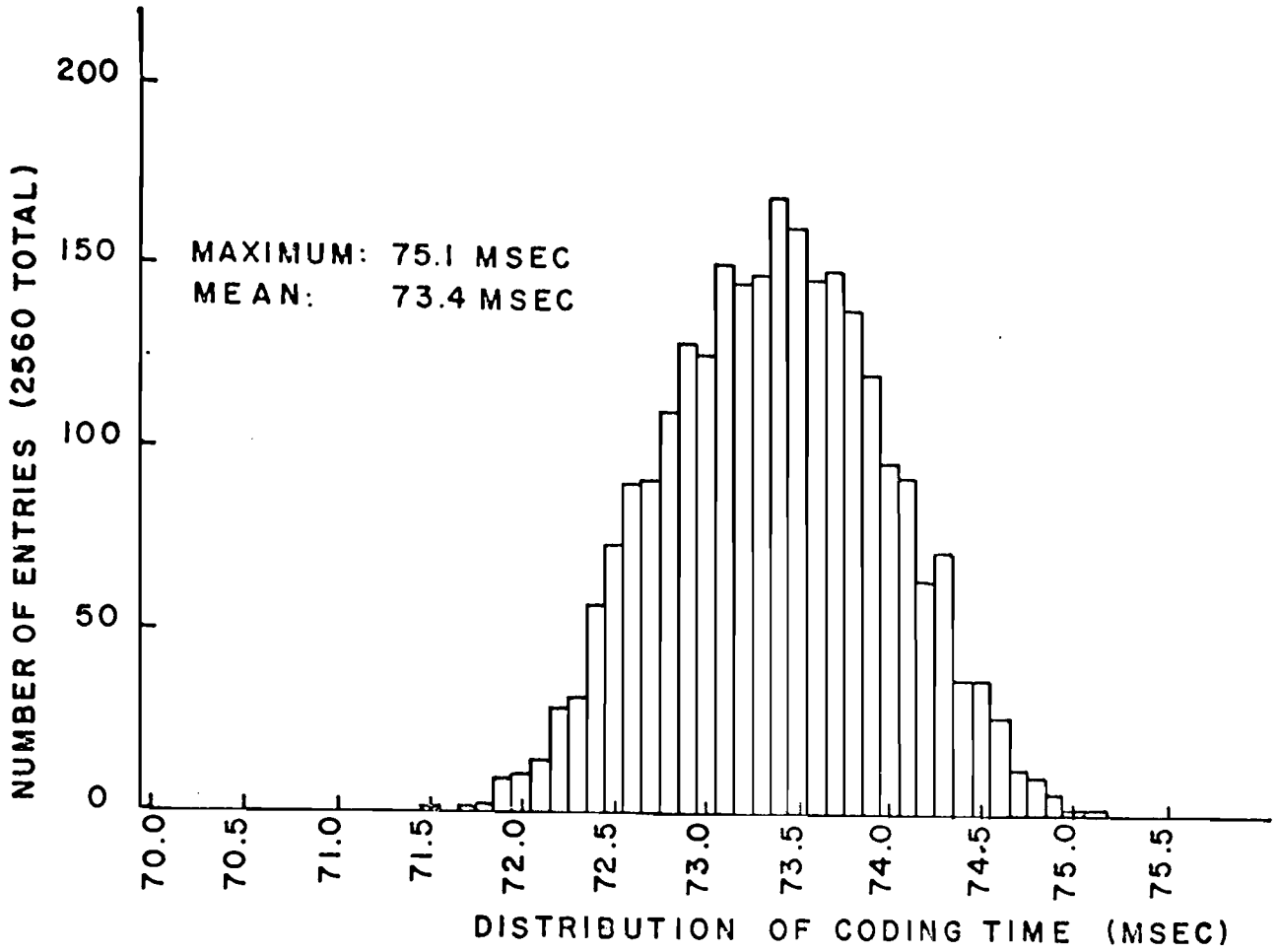

Figure 1

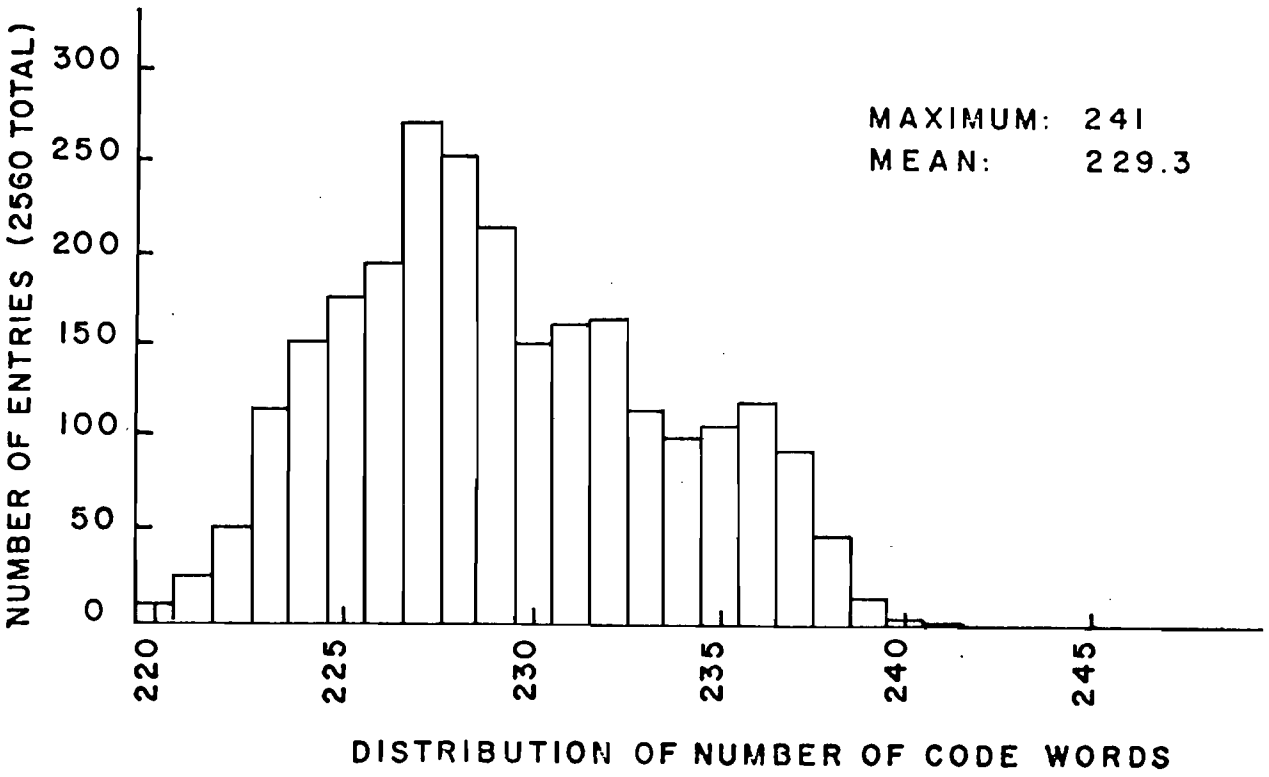

Figure 2

C-19. OPERAS

Personnel: M. D. McDonald, BCL
C. S. Coble, BCL
J. Markham, BCL

Support: RR 00396

OPERAS[1-2], the operator system designed to perform fast and accurate calculations on large amounts of data gathered by the Anger scintillation camera was described in (PR 7, C-12). The initial use of the system was for dead-time correction, background subtraction, and correction for non-uniformity of the spatial response of the camera face. Approximately 100 frames of data were so processed in 45 minutes; this time was considered excessive. OPERAS underwent modifications to produce the version currently in use. The time required for the above calculation with the new version was reduced to 5 minutes.

[1] M. D. McDonald, C. S. Coble, and J. Markham, "OPERAS, Operator System," BCL Monograph No. 162, September, 1971.

[2] M. D. McDonald and C. S. Coble, "Operator System," in Computer Processing of Dynamic Images from an Anger Scintillation Camera, Chapter 14, Proceedings of a workshop held at Washington University, edited by J. R. Cox and K. B. Larson, January, 1971. To be published by the Society of Nuclear Medicine.

C-20. Programs for Nuclear Medicine

Personnel: R. L. Hill, BCL
J. M. Baker, BCL
J. Markham, BCL

Support: RR 00396
AT(11-1)-1653

During the past year several new applications programs have been written for the PDP-12-gamma camera system. These programs, along with others written in previous years, are being used in the continuing projects of the Nuclear Medicine group (see C-11, C-12, C-13, C-14, and C-15).

TLC - This program calculates the total lung capacity by the method of Barnhard[1]. Several measurements are made from chest radiographs of a patient. These values are entered into the computer and the total lung capacity is calculated. This program is written in FOCAL-12, an interpretive language.

TTY32 - This program generates hardcopy output of data arrays collected from the gamma camera. The user specifies which portion of an array is to be printed. This program is written in FOCAL-12.

SPIRAGNW - A program has been written to collect data from a gamma camera, detecting changes in the transmission of radioactivity through the lungs of a patient during normal breathing. The ultimate goal is to correlate this data with that from ventillation studies (see C-11). Data collection is synchronized with an electronic signal sampled from a wedge spirometer. The spirometer signal is divided vertically into eight equal parts resulting in the collection of sixteen frames, each 16-by-16, eight on the upward slope, eight on the downward slope. The maximum and minimum of the spirometer signal are tracked with a low-pass filtering technique similar to that previously described (PR 6, C-1). Data are collected and superimposed from multiple respiratory cycles. The initial processing has taken the form of comparison of the frames obtained at maximum and minimum inspiration and curve fitting of both the upward slope and downward slope to determine rates of change.

GPPP - This general purpose preprocessor program makes basic corrections to the raw data collected by the general purpose data-collection program (PR 7, C-3). These operations include dead-time correction, correction for non-uniformity of the camera face, and background subtraction; OPERAS (see C-19) is used for all arithmetic operations. The corrected data, which is written on LINC tape, is then used for any further calculations.

(1) J. O'Shea, N. L. Lapp, A. D. Russakoff, R. Reger, and W. K. C. Morgan, "Determination of Lung Volumes from Chest Films," Thorax, 25, 544-549, 1970.

C-21. Calcium Transport in Myocardium

Personnel: G. R. Little, Ph.D., Electrical Engineering
C. F. Peiper, BCL

Support: RR 00396
Washington University

Planned last year was a series of *in vivo* calcium-47 washout studies on myocardium (PR 7, C-27). Due to heavy usage of existing facilities in the Division of Radiation Physics, we have chosen, after a single experiment to modify and continue work in the Engineering Biophysics Laboratories of Washington University. Data from the single experiments were fitted with exponentials and compartmental models are being constructed with recirculation considered(1). *In vitro* experiments are continuing with calcium-47 and strontium-85 on isolated guinea pig right atria, augmenting ongoing research into ion-transport mechanisms in myocardium.

To facilitate data collection in the Engineering Biophysics Laboratories, six data channels and control functions were interfaced to a remote Micro-LINC[2]. The new interface has a dead time of 400 ns and a 100 ms integration period. Much of the software was adapted from a sister system in the Division of Radiation Physics (PR 6, C-9) and all data formats are identical so that new programs will be compatible with both systems. The new system has greatly expedited data collection and management.

[1]K. B. Larson and D. L. Snyder, "Measurement of Blood Flow by External Monitoring of Radiotracers with Interference Due to Recirculation and Perfusion of Adjacent Tissues," BCL Monograph 158, October, 1971.

[2]C. F. Pieper, "Micro-LINC-Gamma Probe Interface," BCL Monograph 169, May, 1972.

D-1. A New Surgical Intensive Care Unit

Personnel: L. J. Thomas, M.D., BCL, Physiology and Biophysics, and Anesthesiology
R. Adams, Barnes Hospital
R. J. Arnzen, BCL
G. J. Blaine, BCL
A. L. Bodicky, BCL
R. E. Clark, M.D., Surgery
M. Evans, Barnes Hospital
V. W. Gerth, Jr., BCL
R. W. Hagen, BCL
J. M. Pexa, BCL
C. F. Pieper, BCL
T. F. Schuessler, BCL
R. N. Tatum, BCL
C. S. Weldon, M.D., Surgery
L. J. West, BCL

Support: RR 00396
Barnes Hospital
Washington University

A new cardiothoracic surgical intensive care unit (SICU) was completed in the past year and is now in clinical use. Collaboration between the Department of Surgery, Barnes Hospital and the Biomedical Computer Laboratory continues toward the goal of completing a computer-based system for monitoring and study of critically ill patients in this facility. Conventional analog monitoring is currently accomplished with equipment chosen with compatibility to the computer system in mind. Most of the developmental efforts for the computer system have been completed and have recently converged in a prototype system located at the Biomedical Computer Laboratory but linked to the SICU in the forthcoming year. Most of the components have now been finalized so that only replication is needed. The following reports in this section summarize the Biomedical Computer Laboratory's activities related to the care of the critically ill.

D-2. The SICU Video Display System

Personnel: V. W. Gerth, Jr., BCL
D. E. Gayou, BCL
R. W. Hagen, BCL
K. L. Kunkelmann, BCL
L. J. Thomas, M.D., BCL, Physiology and Biophysics, and Anesthesiology

Support: RR 00396
Washington University

The SICU Video Display System design has been completed and construction is finished on most of the major components. The graphic channels have been in use for three months in support of the software checkout effort using both the scroll and static modes. In addition, the delayed graphics feature has been tested using specially written diagnostic routines.

As a result of experiments in addition to those previously reported (PR 7, D-7), improvements were made in the graphic generator design to enhance contrast and increase operator usability. Other experiments were performed to aid in the selection of CRT phosphors and optical filters.

In order to improve reliability, the initial plan to use mechanical switching of video signals at the bedside display units has been discarded in favor of electronic switching accomplished centrally under control of the computer. The desired channel is indicated by depressing a solid state switch at the bedside monitor which the computer senses via the communication system; and then executes an IOT instruction to accomplish the pairing of the display channel with that monitor.

The primary time base for the SICU system is derived from the crystal controlled oscillator in the television sync generator in order to maintain synchronism between the video raster and the computer sampling schedule.

D-3. SICU Communications System

Personnel: G. J. Blaine, BCL
D. J. Bax, BCL
C. R. Buerke, BCL
R. W. Hagen, BCL
J. W. Oetting, BCL
J. M. Pexa, BCL
J. B. Sellinger, BCL
L. J. Thomas, M.D., BCL, Physiology and Biophysics, and Anesthesiology

Support: RR 00396
Washington University

The SICU Communications System concept consisting of a Local Bus and Message Shuttles was described in PR7, D-3.

Design and development activity focused on the Local Bus, Local Bus Terminals (LBTs), and special interfaces required for the SICU configuration. The Local Bus and LBTs provide a standard modular digital interface for the acquisition and distribution of data within the care unit[1].

The patient's pysiological signals are conditioned and digitized by interface units located at each bedside[2]. Other special interface units developed include a 16 character digital display using a Burroughs Self Scan, a parameter selection keyboard, and a two-channel strip recorder which can be operated via manual or computer control.

A prototype system including a Local Bus, computer (PC-1200), bedside interface unit, digital parameter select/display, and strip recorder was implemented to permit evaluation of both hardware and software during the development phase. Coaxial cables were installed to link the prototype system, located in the basement of BCL, to the SICU in 2200, Rand Johnson Hospital. The availability of signals from post-surgical patients allows a realistic base for system development.

The current phase of communication activity includes the construction, assembly and test of LBTs and bedside interface units for installation in the SICU, and the design of the Message Shuttle.

[1] G. J. Blaine, J. R. Cox, Jr., and J. M. Pexa, "A Digital Communication System for Clinical Application", submitted to the 25th Annual Conference on Engineering in Biology & Medicine.

[2] J. R. Cox, Jr., R. W. Hagen, and L. J. Thomas, "Interfacing Physiological Patient Information to a Digital Acquisitor System", submitted to the 25th Annual Conference on Engineering in Biology & Medicine.

D-4. The SICU Computer System

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

Support: RR 00396
Washington University

All components of the computer systems for the SICU have been tested independently and have been combined at BCL to provide a hardware configuration ultimately capable of monitoring five patients simultaneously. The system is limited at present to one patient by the lack of peripheral hardware, but construction of the missing items is underway. This configuration has been extensively tested using both on-line data over cables from patients in the SICU and patient data stored on magnetic tape.

Reliability has been excellent with an average of one failure per month in an environment which includes numerous tests and changes. It would appear that when the system is installed in the SICU the reliability should be at least as good.

All special purpose hardware including the digital communication system, video display system, and interrupt control is connected to the PC-1200 I-O Bus. No changes in the CPU have been required.

D-5. SICU - Programs and Algorithms

Personnel: L. J. Thomas, M.D., BCL, Physiology and Biophysics, and Anesthesiology
R. E. Clark, M.D., Surgery
R. W. Hagen, BCL
C. F. Pieper, BCL
R. N. Tatum, BCL
L. J. West, BCL

Support: RR 00396
Washington University

Algorithms have been devised and PC-1200 programs written for computer monitoring and study of the critically ill. Functions include sampling and analysis of physiologic data; generation of digital displays of derived parameters; generation of video monitor displays of arterial pressure and the ECG waveforms complete with alphanumeric labeling, parameter boundry limit caution notices, and patient information; generation of selectable digital displays of parameter values; driving of recorders for permanent documentation of arterial pressure and ECG waveforms; and keyboard entry of control information.

The overall program provides for continuous and simultaneous monitoring of five patients with a single PC-1200 minicomputer fitted with an 8K memory. The basic functions cited above are accomplished by a permanently resident program occupying 4K of core. The remaining 4K is allocated for other functions such as data collection for trend analysis and physiologic studies, for which programs are now being written.

The physiological variables under continuous scrutiny are listed below with their sampling rates.

Variable	Samples per second
Electrocardiogram	240
Arterial blood pressure	120
Central venous pressure	30
Left atrial pressure	30
Airway pressure	30
Respiratory gas flow	30
Temperature	7.5

Derived parameters available for digital display currently include: heart rate, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, mean central venous pressure, mean left atrial pressure, tempterature, respiratory rate, tidal volume, peak inspired airway pressure, and total (lungs plus chest) dynamic compliance. Provision has been made for five additional parameters to include blood-gas values, arterio-venous oxygen content difference, and cardiac output.

Particular attention has been given to developing parameter-derivation algorithms which will function reliably when confronted with the sub-optimal waveforms commonly encountered in clinical settings. To this end, the algorithms have been thoroughly tested using on-line signals obtained via coaxial cables run from the cardiothoracic intensive care area in Barnes Hospital to a mock-up system operating in the BCL building. In addition, challenging ECG waveforms were selected from an extensive library of data recorded from the Coronary Care Unit. These proved to be extremely valuable in testing and adjusting the QRS detection algorithm to a level of gratifying reliability.

D-6. SICU - Transducers and Signal Conditioners

Personnel: R. W. Hagen, BCL
R. J. Arnzen, BCL
A. L. Bodicky, BCL
T. F. Schuessler, BCL
L. J. Thomas, M.D., BCL, Physiology and Biophysics, and Anesthesiology

Support: RR 00396
Washington University

A primary consideration in the design of the SICU monitoring system required that the transducers and signal conditioners be safe and reliable[1]. To assure the achievement of these requirements detailed testing has been conducted on the system components. The evaluation of transducers and signal conditioners necessary to monitor the parameters indicated in PR 6, D-2 has been completed and most components have been in use since October 1971. A BCL monograph discussing the evaluation of physiologic pressure transducers is nearly complete. This evaluation included comparative testing of commercially available unbonded strain gauges as well as differential transformer and semiconductor strain gauge transducer types.

Frequency response tests have been conducted on the pressure monitoring system used in the cardiac catheterization laboratory. A mechanical damping device, which promises to improve the frequency characteristics of this system as well as other similar systems, has been designed and is being tested.

A transducer mounting manifold was designed to systematically arrange the bedside transducers in a manner that simplifies their setup and calibration. A prototype has been evaluated and the manifold is being redesigned to correct the problems discovered.

[1] J. R. Cox, Jr., R. W. Hagen, L. J. Thomas, "Interfacing Physiological Patient Information to a Digital Acquisition System," submitted to the 25th Annual Conference on Engineering in Biology and Medicine.

D-7. SICU - Mechanical Systems

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

Support: RR 00396
Barnes Hospital
Washington University

In October of 1971 mechanical and architectual planning and construction of an intensive care unit for cardiothoracic surgery at Barnes Hospital was completed (see PR 7, D-6). After six months of use the unit has been successful on the basis that no serious complaints have been registered from any of the personnel carrying on activity within the unit. These include doctors, nurses, electronic technicians and the patients themselves.

Work remaining for the overall completion of the SICU includes the manufacture and installation of components relating to the computer monitoring system and its associated communication system. At present the mechanical design of equipment for this system has been essentially completed. There remains, however, the fabrication in our shop of this equipment and its installation within the unit.

D-8. SICU - Monitoring Instrumentation Installation and Personnel Training

Personnel: R. W. Hagen, BCL
R. Adams, Barnes Hospital
D. J. Bax, BCL
A. L. Bodicky, BCL
R. E. Clark, M.D., Surgery
K. L. Kunkelmann, BCL
T. F. Schuessler, BCL

Support: RR 00396
Barnes Hospital
Washington University

The SICU analog monitoring instrumentation was installed in October 1971 and has been in operation since then. Each bedside system contains a digital voltmeter, dual trace oscilloscope, syncronized defibrilator, analog heart rate computer, signal amplifiers and transducers. EKG and arterial pressure are displayed on the oscilloscope with central venous pressure,

temperature, heart rate and left atrial pressure being selectively displayed on the digital voltmeter. The interconnecting cables and switching modules were assembled and the instrumentation system was installed by BCL personnel. Informal training has been conducted to instruct nursing personnel in the use of the monitoring system. Routine system calibration is being performed by BCL technicians.

D-9. SICU - Electrical Safety

Personnel: R. R. Pfeiffer, Ph.D., Electrical Engineering
R. Adams, Barnes Hospital
R. M. Arthur, Ph.D., Electrical Engineering
R. E. Clark, M.D., Surgery
R. W. Hagen, BCL

Support: RR 00396
GM 01827
HS 00074
RR 06115
Barnes Hospital
Washington University

The Electrical Power Distribution System in the surgical intensive care unit was designed to provide an electrically safe and noise free environment[1]. The design incorporated considerations of the electrical aspects of all exposed metallic surfaces within individual patient rooms. Electrical considerations encompassed distribution of 115 volt emergency power and regular power and of 208 volt power, plumbing, utilities (oxygen, compressed air, and vacuum lines), monitoring equipment, the data communications system and building structures. The design maximizes the likelihood of realizing an equipotential patient environment and eliminates noise due to ground loop configurations. It is compatible with new construction codes and economical to attain. Basically the system uses tree structured grounding with each patient room electrically isolated from building structure except at a single central point. At this point all branches of all trees: electrical, utility, and plumbing are electrically tied together.

[1] R. M. Arthur, R. R. Pfeiffer, and R. E. Clark, "Comprehensive Intensive Care Unit Electrical System Design," submitted to the 25th Annual Conference on Engineering in Biology and Medicine.

D-10. Algorithms for the Calculation of Blood Parameters

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

Support: RR 00396
HL 00082

The algorithms developed for deriving a variety of blood parameters from laboratory values (see PR 7, D-9) were refined, a FORTRAN IV version was completed and tested, and a publication[1] was prepared. In addition, a related algorithm was developed for calculating standard bicarbonate for the same system.

[1] L. J. Thomas, Jr., "Algorithms for Selected Blood Acid-Base and Blood Gas Calculations," J. Appl. Physiol. 33, pp. 154-158, July, 1972.

D-11. A Photography System for a Prosthetic Heart Valve Tester

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

Support: RR 00396
HL 13803
Washington University

A time-lapse photography system has been developed to produce a photographic history of a prosthetic heart valve undergoing accelerated fatigue testing up to 34 cps. The system contains a modified 8 millimeter movie camera, repeat cycle timer, high intensity strobe light, valve position transducer (PR 7, D-13), and digital control circuit. Improvements are being made in the modified camera to give more reliable operation. The system takes one picture per hour. Each succeeding photograph shows the valve advanced 1/24th of a full valve cycle. Thus a film is produced showing the valve in slow motion. When projected at 24 frames/sec., the film shows 24 hours of testing in 1 second. This aids the valve designer in determining how and when the prosthetic heart valves fail under controlled conditions of flow, pressure and cycle rate.

D-12. Automated Perfusion System

Personnel: P. S. Berger, BCL
C. R. Buerke, BCL
R. E. Clark, M.D., Surgery

Support: RR 00396
Washington University

In order to reduce the technician effort and improve the reliability in a perfusion system, various elements of the system have been or will soon be automated into a closed-loop control arrangement. To date, an automated mean flow pump based upon a volume displacement principle has been controlled successfully. This allows minimum differential pressure across the membrane oxygenator used in the system and guarantees equal flow rates on the venous and arterial sides of the bypass system. The volume displacement error is used to control the rate of the arterial pump and is slaved in closed-loop fashion to the venous pump in the two pump set-up.

Future plans include automating the first (venous) pump by using an identical control circuit with appropriate pressure sensing elements. The purpose of this is to regulate the flow of the venous blood out of the vena cavae using negative venous pressure as a control parameter.

D-13. A Ventilator Monitor

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

Support: RR 00396
Washington University

A ventilator monitor has been designed which alerts attending personnel when the respiratory rate and/or peak pressure fall below preselected limits. The monitor is connected to the patient mask or endotracheal tube with a T piece. A small tygon tube is attached between a port of the T piece and a pressure switch installed in the monitor unit. An audio and visual alert occurs if: 1) the ventilator peak pressure does not exceed a limit, 2) the ventilator rate does not exceed a limit, 3) the tubing between the patient and ventilator is disconnected. This ventilator monitor has been operating successfully for six months in the cardiothoracic operating room.

D-14. Measurement of Cardiac Output

Personnel: R. W. Hagen, BCL
A. L. Bodicky, BCL
R. E. Clark, M.D. Surgery
W. H. Cloud, BCL

Support: RR 00396
Washington University

Recent studies conducted by numerous investigators using the thermal dilution technique for determining cardiac output have been promising and an effort has begun to utilize this method in the SICU. Instrumentation is being developed for use with the Swan Ganz flow-directed thermodilution catheter. An instrument containing a bridge, amplifier and integrator has been designed and tested in dogs. The dye dilution method is being used as the control in the tests. Currently the system is being redesigned with a more stable amplifier so that a smaller bolus (5ml) of room temperature saline can be used. In addition, an analog divider is being added so that the value for cardiac output can be read directly.

E-1. Revision of Teleprocessing Programs

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

Support: RR 00396

During the past year, host programs which implement communications between the host computer, the University's IBM 360(Model 50), and the various small computers at the Medical School, have been rewritten. The revised programs have been in operation since the middle of February. There were several things that we wished to accomplish:

1. The size of the host partition required by the program was reduced. This has been cut from 24K to 20K bytes of memory. Many additions had been made to the initialization procedures which were needed only once, so they were gathered into one program which is deleted upon its completion.

2. Space was released in the resident portion of the Operating System which has a record of all data sets referenced by active jobs. The number of data sets keeps increasing, so the method of opening data sets was revised in such a manner that dummy references are required for only as many data sets as might be simultaneously in use. Currently we are using six. Three added advantages followed from this: the size of the card deck now used to bring the program into execution is about a third of what it was; data sets can be compressed, etc. from other partitions while the program is active; and program termination because of a mismatch between the data set definition cards in the program deck and existing data sets is eliminated.

3. The procedure required to change the number of data lines in use was simplified. This can now be accomplished by changing one job control statement and one card in the portion of the program called PC BLOCKS and reassembling it.

4. Steps have been taken to ease the proposed change over from the IBM 2701 to the Memorex interface to the data lines (see E-3). Subroutines were written to handle all data line and disk operations, and macros were provided to set up all calls to them. Thus, any program changes required are localized and should be more easily debugged. This procedure also contributed to the reduced space requirements of the program by eliminating redundant code in the various function modules.

A new function module (CVT) has been added which will convert an existing member of a file from ASCII to EBCDIC or back. Primarily this permits interaction between CPS and the communications system.

Flow diagrams of all the programs with detailed explanations are now available in BCL Monograph 104C[1]. Used in conjunction with the Manuscript listings (BCL Monograph 104B[2]) it should be of considerable assistance in adapting the program to other environments, or in otherwise altering it.

[1] D. Bridger and E. Van Patten, "Program Description - Collaborative Mode PC Support Using OS/360", BCL Monograph No. 104C, to be published.

[2] D. Bridger and E. Van Patten, " Manuscript Listing - Collaborative mode PC support using OS/360", BCL Monograph No. 104B, April, 1971.

E-2. Teleprocessing for the Classic LINC

Personnel: E. Van Patten, BCL

Support: RR 00396

A new program is being written for the LINC which roughly parallels the PC Utility program. It will facilitate the maintenance of IBM 360 (Model 50) disk files and the storage and retrieval of data, and will make more of the additions and improvements to the Model 50 Telecommunications programs readily available to the LINC users. In conjunction with this, the meta command in the LINC-PC system which will store a PC assembled program on the Model 50 disk, is being expanded to allow storage of the contents of the LAP6 manuscript area also. Changing of data that are in alphabetic mode will be expedited by having LAP6 editing features available. The ease of getting a printout of such data should also prove useful.

E-3. Maintenance of Networks for Teleprocessing

Personnel: R. H. Greenfield, BCL

Support: RR 00396

The switching system for collaborative data processing which has been reported on previously (PR 7, E-3) reached its originally designed maximum capacity of servicing ten remote small computers. Engineering work was in progress a year ago to expand the system capacity to a maximum of twenty stations. This work was dropped due to a decline of traffic on the system, a decline of demand for connection to it, and the uncertain status of our host computer the IBM 360 (Model 50).

In the fall of the year, the Model 50 underwent several drastic hardware changes which caused frequent outages of service. The host computer underwent the replacement of IBM mass core storage, disk drives, tape units, and communications controllers with plug to plug compatible non-IBM devices. Those changes when finally completed, resulted in a more powerful host computer with a much improved cost/performance ratio.

Decline in usage was also a result of the upgrading and augmentation of two Spear Program Console (PC) Systems which were heavy users of the system for program storage. The Catheterization Laboratory computer was upgraded to support LINC tape. The Radiation Treatment Planning machine was augmented with the addition of an Artronix PC-1200 which supports LINC tape. These two facilities thus no longer extensively utilize the host computer for program storage.

The fall and winter saw much improvement in the physical integrity of the system. The host modems were relocated to a more environmentally favorable location and replaced with five identical bench checked units, one unit being a spare. Much of the wiring which constitutes the system was replaced and reorganized. Southwestern Bell, the local AT & T operating company, completely rewired their circuits both at our basement switching center and at the Computing Facility. BCL has also upgraded a good portion of its wiring. This equipment and wiring overhaul has resulted in a more dependable, more easily maintainable system.

The IBM 2701 Type III Terminal Adapter now used for our telecommunications will soon be removed. The Memorex 1270 Terminal Control Unit, which is currently handling all other telecommunications with the Model 50 will then be modified to handle the load from the IBM 2701. The substitution of this Memorex Control Unit will result in a significant monthly operating cost reduction.

E-4. Digital Communication Systems

Personnel: D. L. Snyder, BCL
G. J. Blaine, BCL
W. S. C. Chang, Ph.D., Electrical Engineering
R. O. Gregory, D.Sc., Electrical Engineering
W. R. Lang, BCL

Support: RR 00396
F 44620
GK-32239

A procedure for designing signals for binary communication over time dispersive channels, such as cables and telephone lines, has been developed. The design procedure is sufficiently general that practical contraints on the

signals can be incorporated; these include bandwidth, energy, and peak constraints. The procedure is readily implemented for computational or numerical determination of the signals that minimize the binary error probability subject to constraints. Details of the design procedure are reported in BCL Monograph No. 160[1].

We have begun the design and construction of an all solid-state, optical, digital communication system. It is planned that this system will operate at a one megabit per second rate over an atomospheric path of about 550 yards from the roof of the Jewish Hospital to the roof of the Barnes Hospital. The roof terminals will be connected by cable to the cardiac care units of each hospital. This communication facility will be used to communicate digitized electrocardiographic data at sixty times real time from the Jewish Hospital CCU to the Barnes Hospital CCU; the data will then be relayed by cable to BCL for processing.

(1) D. L. Snyder and G. J. Blaine, "Signal design for channels with known time dispersion," BCL Monograph No. 160; December, 1971. To be presented at the 1972 National Telecommunications Conference, Houston, Texas, December, 1972.

E-5. Multipair Transmission Line Studies

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

Support: RR 00396

Successful application of digital communications technology requires careful specification of a transmission media. The SICU Communications System (D-3) utilizes a 48-pair transmission cable for the acquisition and distribution of digital data and control signals at mega-word rates.

Studies were conducted to determine the effects on transmitted signals of drivers, receivers, interline cross-talk, line attenuation, and line termination for multiconductor cables. Experiments were performed to measure the effects of tapping the multiconductor cable via printed circuit boards, edgeboard connectors, and short lengths of wirewrap interconnections to multiple drivers and receivers.

Application of transmission line theory has resulted in a simple model to explain and quantify the effects of both near-end and far-end cross-talk for multipair cable used in a single-ended configuration.

A skin-effect model for a single pair transmission line was utilized to predict both pulse distortion and attenuation as a function of transmission distance. A FORTRAN program was written to perform the analysis in the frequency domain. The single input parameter for the calculation is the half power frequency for 100 feet of cable.

F-1. Clinical Evaluation of Cardiac Catheterization Computer System

Personnel: R. S. Rosenfeld, M.D., Medicine
W. V. Glenn, M.D., Public Health Service
G. C. Oliver, M.D., Medicine

Support: RR 00396
HL 05332
HL 11034
Washington University

Experience gained from the extensive use of the programs for cardiac catheterization data analysis led to the realization that improvement was needed in speed of system response and in the niceties of the report format. The Spear Programmed Console (PC) was modified (see F-2), greatly improving the speed of analysis and report generation, and often allowing the results to be available before the patient leaves the catheterization laboratory.

A technician currently performs all of the data collection tasks and is responsible for maintaining files of patient data. There are two files. One is a summary of analysis results on each patient. This file is kept on LINC tape in the catheterization laboratory (100 patients per tape) where it is available for rapid retrieval. The other file contains all of the digitized data collected on each patient and is stored at the IBM 360 (Model 50) computer on large magnetic tapes. This file system makes extensive use of the telecommunications systems with the Model 50 (see E-1). Data has now been collected on over 400 patients.

The cardiologists in the catheterization laboratory make extensive use of the results of the computer analysis of data. They have found that considerable time is saved on procedures which require extensive analyses. The pattern recognition scheme currently being used (the human brain) has resulted in a high degree of accuracy. The analysis task is simple enough so that it is often performed by the laboratory technician.

F-2. Hardware Modifications of the Catheterization Laboratory Computer

Personnel: B. F. Spenner, BCL
C. R. Burke, BCL
J. G. Green, BCL
R. S. Rosenfeld, M.D., Medicine

Support: RR 00396
HL 05332

The modification of the Spear PC located in the catheterization laboratory was performed to increase machine efficiency and to establish program compatibility between the Spear PC and the Artronix PC-1200.

Changes were made in the (1) interrupt, (2) JMP and branch instructions and (3) keyboard operations. LINC tape and a Tektronix Hard Copy unit were added to the system. The operational changes provide software compatibility between the Spear PC and the PC-1200 except for the use of interrupts.

LINC tape units were added to the catheterization system to provide a medium-speed mass-storage device. The LINC tapes are used for temporary storage of all collected patient data. The addition consists of a LINC-4 tape controller (PR 7, F-14) and an interface.

The Tektronix Hard Copy unit was added to the system to provide a device capable of producing a printed page at speeds which are compatible with the needs of the catheterization laboratory.

F-3. Revision of the Catheterization Laboratory System

Personnel: W. V. Glenn, M.D., Public Health Service
J. M. Baker, BCL
G. C. Oliver, M.D., Medicine
R. S. Rosenfeld, M.D., Medicine

Support: HL 05332
HL 11034
RR 00396
Washington University

Revision of the programs for analysis of cardiac catheterization data was undertaken for the following reasons: (1) Portions of the report were not easily understood by persons not intimately connected with the laboratory. (2) There were inconsistencies in the operation of the system from a user point of view. (3) The program itself was unwieldy and difficult to modify. (4) The varihardware changes (see F-2) necessitated appropriate software modifications.

The revised software system has a modular structure. A protocol has been set up to guide the construction of modules and the interactions between modules. There is a common utility package which includes double-precision arithmetic routines (see J-16), analog to digital conversion, a standard method for handling information transfer to and from LINC tape, and an executive which handles the overlaying of and transfers between the many modules in the system. In addition, PC Q&A[1] has had modifications which include the use of a 5-by-7 character generator, the specification of character size in the text string and the use of text string arguments to enable underlining. These changes should make future modifications and additions to the system much easier to implement.

The programs themselves have been modified to allow the collection of larger amounts of data. In addition, the conditions under which the data were obtained (e.g. rest, exercise, etc.) can be specified. Certain editing features have been added. The use of special function keys has been made more consistent. The output format has been totally revised and is now suitable for use as a final report to be made a part of the patient's permanent hospital record. This revised version is expected to be available for routine use in August, 1972.

[1] M. D. McDonald, "PC Q&A," BCL Monograph No. 127, February, 1970.

F-4. Pressure Monitoring Instrumentation for Evaluating Angiographic Injection Systems

Personnel: R. W. Hagen, BCL
N. Schad, M.D., Radiology

Support: RR 00396
Washington University

An instrumentation system was designed and assembled to measure the dynamic pressures developed within catheters during angiographic injections. This pressure is of interest when evaluating angiographic injection systems and procedures. A charge amplifier was designed to condition the output of a piezoelectric pressure transducer. During tests the high pressure waveshapes were recorded on a storage oscilloscope and photographed for analysis. In vitro tests have been conducted using various catheters and interconnecting tubes. Additional testing is planned with other injectors and in dogs.

G-1. Mass Spectrometer Analysis System

Personnel: W. F. Holmes, BCL
D. J. Bates, A.B., Biochemistry
W. H. Holland, A.B., Psychiatry
B. L. Shore, B.S., Applied Mathematics and Computer Science
H. J. Weiss, B.S., Applied Mathematics and Computer Science

Support: RR 00396
CA 10926
GM 01311
MH 07081
MH 20717
Washington University

The first phase of development of the mass spectrometer computer system[1] (see also PR 7, F-6) was completed with the incorporation of a tabular listing program for mass spectrum scans. One or more consecutive scans can be tabulated as a list of the masses found and their peak abundances. Options include a separate list of the N largest masses, selection of mass range and abundance threshold, and normalization to a selected mass or the greatest one. The program is designed to work with three types of printers, an ASR 33 Teletype (ten characters/sec), a REPCO 120 printer (one line/sec) or a Versatec 1100A electrostatic printer/plotter (eight lines/sec). The program automatically selects the fastest printer attached to the PDP-12 in use, and adjusts the number of tabular columns printed so as to make full use of the printer's line width.

With the Versatec printer, typical scans can be listed in two seconds, which is faster than they are acquired, eliminating the final bottleneck in the automation of mass spectrometer data acquisition and reduction.

A REPCO printer interface for the PDP-12 was designed as an extension of the Model 50/PDP-12 telephone communication interface (see PR 7, E-2). A common crystal oscillator is used, and the REPCO print character logic is very similar to the transmit character logic of the communication interface.

A new and more flexible mass spectrum data format was devised, allowing a compression of two or three-fold in typical cases, with a partial or complete loss of calibration information, but full retention of nominal mass and peak abundance. The revised format will facilitate automatic identification of mass spectra by searching reference files on PDP-12 LINC tape (see G-3). A program has been written to convert and transfer selected scans from an old format tape to a new format tape, which also serves as a convenient method of sorting and collecting useful spectra. Background spectra can be subtracted using the new format, and a Versatec plotter program is nearly completed.

[1] W. F. Holmes, W. H. Holland, J. A. Parker, "A Display Oriented Mass Spectrometer-Computer System," Analytical Chemistry, 43, 1806-1811, 1971.

G-2. Multiple Ion Detection for Mass Spectrometry

Personnel: W. F. Holmes, BCL
W. H. Holland, A.B., Psychiatry
B. L. Shore, B.S., Applied Mathematics and Computer Science

Support: RR 00396
MH 20717
Washington University

A precision computer controlled variable high voltage source has been designed for the LKB-9000/PDP-12 mass spectrometer computer system (see PR 7, F-9). The voltage source is modular, which facilitates upgrading the system as higher quality components become available. The source consists of four sections, computer interface, D/A converter, high voltage amplifier, and a fixed high voltage power supply. The computer interface allows a two-word twenty-four-bit output from the computer to be transferred to a storage register with independent transfer to the D/A converter. A twelve-bit input register is available as a by-product, for upgrading the PDP-12 A/D converter from ten bits. A fifteen bit Fluke 4216A D/A converter provides a ±16 volt computer-controlled output, which is amplified to ±500 volts by a BE-134 booster amplifier. This voltage source is grounded at one terminal and connected in series with a floating, but otherwise standard 3500 volt mass spectrometer power supply.

A test program has been written to check the accuracy, response time and drift of the system. The program creates a precision generator of DC levels, square waves, and linear ramps. DC levels and waveform amplitudes are specified to a resolution of one part in 2^{15} (one millivolt at the output of the D/A), while the computer clock is used to specify waveform periods in milliseconds. The system as it now stands appears suitable for a computer switched multiple ion detection system where a resolution of 0.1 mass unit is usually sufficient, equivalent to a stability of one volt at mass 350. The booster amplifier is the major source of drift and nonlinearity, and will be replaced before any attempts at peak matching are made.

In order to monitor total system drift, a second test program has been completed which generates a ten volt sweep centered at any of five masses, and samples, stores, and displays the ion signal. Thus individual fragment ions can be examined for peak shape and drift. This program will be used as part of a multiple ion detector program for initial voltage focussing on the fragment ions, and for providing a drift detector during the course of an experiment. By monitoring a fragment ion of known mass during an experiment, a feedback loop can be set up using visual or automatic control, in which the fragment ion forms an internal standard for drift control.

G-3. Mass Spectrometric File Search

Personnel: R. Inselberg, BCL
W. F. Holmes, BCL

Support: RR 00396
CA 10926
Washington University

A set of FORTRAN programs for mass spectrum file manipulation and searching have been written and tested. The file manipulation programs permit interconversions between IBM tape files and spectra on LINC tape. There are two distinct programs.

1. Reference mass spectra on IBM Tape are read by a Model 50 FORTRAN program, converted to the PDP-12 LINC tape format, and stored on a disk file. The LINCOMM communication program (see PR 5, E-4) is used to transfer the spectra over a telephone line from the Model 50 to a LINC computer and onto LINC tape. The spectra can then be displayed, plotted, and listed by the PDP-12 mass spectrometry system (see G-1). The standard mass spectrum reference files are large and heterogeneous (such as the Mass Spectrometry Data Center file of 9628 spectra). This program allows smaller subfiles to be created for local use within the PDP-12.

2. LINC tape spectra are sent by the LINCOMM program to the Model 50 disk file. Selected spectra can then be converted to a standard format for further use. A listing program with averaging and subtraction of background scans is available. The format is suitable for use by other mass spectrometer groups, providing a method of distributing mass spectra obtained at Washington University. The reformatted LINC tape spectra can also be used as input to the file search program described below.

A file search program was developed within the Model 50. This was primarily a feasibility study, using the flexibility of FORTRAN to interconvert between various data formats and to test different search algorithms. Selected portions of the reference spectra tape are condensed so that only the two largest peaks in every fourteen mass units are used. These condensed spectra are stored on a search tape in binary, so as to eliminate the time consuming conversions inherent in format controlled FORTRAN read statements. The search program matches a spectrum on the disk file (normally obtained from LINC tape) against each spectrum on the search tape. The matching formula is simply the sum of the absolute values of the difference in peak abundance at each mass divided by the sum of all the peaks in both spectra and with this quotient and subtracted from unity. Thus a perfect match is one, and a complete mismatch with no peaks in common is zero. The search program produces a sorted list of the best match values, along with the name of each compound. This program was tested by preparing a number of spectra with the LKB-9000 mass spectrometer, and sending these to the Model 50 as discussed above. Various sections of the reference tape were condensed into search files of three hundred spectra to save computing costs. However, these subfiles generally contained groups of compounds closely related to the search compound. In general the search compound had the highest match, occasionally

the next highest. The higher match values generally corresponded to compounds similar to the search compound, which is very useful, since the compound of interest may often be missing from the file. The results obtained indicate that searching of mass spectra files within the PDP-12 is practical, using reference LINC tapes containing a few hundred spectra.

G-4. Biochemical Kinetic Simulation and Data Analysis

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

Support: RR 00396
AM 13332
GB-26483X
GM 01311
Washington University

These programs are an outgrowth of the one previously described (see PR 7, F-10). Since kinetics has been a useful tool in elucidating many aspects of the mechanism and regulation of enzyme systems, we have developed a general kinetic simulation and curve fitting system for use on a PDP-12 equipped with floating point hardware[1]. The system consists of two major programs: a compiler and a simulator.

The compiler takes a user supplied kinetic mechanism and sets up subroutines for the numerical integration of the differential equations appropriate to that mechanism. These are then filed on LINC tape for use by the simulator. The simulator does the integration set up by the compiler, giving the concentration of any species in the mechanism as a function of time. The concentration versus time curve for any species chosen in the mechanism can be displayed by itself or on a background of real data acquired by the program described below (G-5). In this latter mode the program can be used for visual curve-fitting to the actual data, since the recalculation and output of the simulated curves is rapid enough to allow the user to exercise control over all the parameters of the kinetic mechanism. Any of the display graphs can be plotted on a Versatec 1100A electrostatic plotter, along with a printout of the mechanism and the kinetic parameters, at a rate of about ten seconds/graph.

The program has already proved useful in the analysis of data on the enzyme glutamic dehydrogenase, whose velocity shows a complex time dependence. It was found that fitting several time curves with different initial substrate concentrations to the same rate constants provided a much more stringent test of alternative mechanisms than fitting constants to a single time curve. The results were fit to a mechanism involving several slow, substrate dependent conformational

changes which partially inactivate the enzyme at high substrate levels. In addition, the results of that analysis were used to predict the enzyme's behavior under different conditions of enzyme concentration and those predictions have subsequently been verified.

(1) D. J. Bates and C. Frieden, "A System for Computer Analysis of Enzyme Mechanisms," Federation Proceedings, Vol. 31, p 467, 1972.

G-5. Stopped Flow Data Acquisition

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

Support: RR 00396
AM 13332
GB-26483X
GM 01311
Washington University

Programs and hardware have been completed (see PR 7, F-11) for the transfer of data from a Durrum-Gibson stopped-flow apparatus to the PDP-12 computer. The percent transmission data are temporarily collected on a Hewlett-Packard 3960A FM tape recorder for later play-back into the computer, eliminating the need for on-line computer use. This data is then picked up by the PDP-12, converted to optical density units as a function of time, and filed on digital LINC tape. The storage format is such that the data is accessible by the simulation programs described above (see G-4) and by FOCAL-12, a conversational language for the PDP-12.

G-6. Ultracentrifuge Analysis

Personnel: R. Inselberg, BCL
S. R. Holmes, A.B., Biochemistry
W. F. Holmes, BCL

Support: RR 00396
Washington University

The sedimentation equilibrium analysis program for the analytical ultracentrifuge (see PR 6, F-3) has recently been revised. As before, curves are traced into the PC with the rho-theta transducer and transmitted

to the Model 50 for analysis. The data are adjusted according to a calibration table, and the logarithm taken. The slope of the resulting data is proportional to the molecular weight.

Complex proteins are generally composed of subunits which reversibly dissociate under some experimental conditions. Such behavior is sometimes part of the in vivo control properties of the protein. Thus much work with the ultracentrifuge involves the study of partially dissociated proteins. The degree of dissociation is concentration dependent. Since the protein concentration in an ultracentrifuge cell at sedimentation equilibrium varies from zero at the meniscus to fairly high concentrations at the bottom, the variation of molecular weight with protein concentration and rotor distance becomes an important parameter to measure.

The original program allowed the experimenter to select pairs of points on the raw data curve with the rho-theta. Each pair of points was used to specify an interval for a linear least squares fit to the reduced data. This involved considerable guess work, often raising more questions when the results were seen after processing. Therefore, a continuous derivative approach has been taken.(1) The logarithmic curve is fit at every two data points to a quadratic equation centered at that point and extending five points on either side, using a best least squares fit. The slope of the quadratic equation at the center point is used to calculate the molecular weight at that point. Since the fitting procedure requires only the calculation of a weighted average, the calculations for the entire curve proceed quite rapidly and are repeated for intervals of ten and fifteen points on each side of the center points. Three graphs are printed of molecular weight versus rotor distance and protein concentration (as optical density), yielding much more detailed information than before at no increase in computing time.

(1) A. Savitsky and M. J. E. Golay, "Smoothing and Differentiation of Data by Simplified Least Squares Procedures," Analytical Chemistry, 36, 1627-1639, 1964.

H-1. A Mathematical Model of the Mechanics of the Cochlea

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

Support: RR 00396

Work has continued on a mathematical model of the mechanics of the cochlea (see PR 6, F-14 and PR 7, F-18). The model includes the effects of viscosity, the three dimensional motion of the cochlear fluid, and the interacting forces in the basilar membrane. All physical parameters used in the model except the basilar membrane damping coefficient are obtained from the experimental measurements of Bekesy and Wever, or derived from basic hydrodynamic equations.

Beginning with the basic hydrodynamic equations, an integral equation is derived to describe the cochlear boundary value problem. By using Green's function techniques and by transforming the integral equation into a differential equation, the model finally takes the form of a second order differential equation, which with its boundary conditions describes the pressure difference across the basilar membrane. A separate expression relates the pressure difference to the basilar membrane motion.

Many results computed from the model are in good agreement with experimental measurements of Bekesy, Johnstone, et al., and Rhode, and also show characteristics similar to those indicated by data from cochlear microphonic voltage and auditory-nerve fiber responses.

A computer model based on this mathematical model will be developed for future studies in hearing and deafness. This computer model, implemented with the aid of macromodules will be used to study the perception of complex sounds such as speech (see H-2).

H-2. A Speech Analysis/Synthesis System

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
J. R. Cox, Jr., BCL
J. D. Miller, Ph.D., Central Institute for the Deaf
B. F. Spenner, BCL

Support: RR 00396
NS 03856

Work on a speech analysis/synthesis system has started. This system is being developed as a research tool for generating speech-like sounds for psychoacoustic experiments and to aid in investigating a wide range of problems in hearing and deafness such as studies of deaf speech, the development of speech training aids, the development of clinical tests pertaining to speech perception, studies of linguistic features, and studies of models of the ear and vocal tract. It is intended that the system will provide a highly interactive environment for the experimenter so that relatively large quantities of speech can be analyzed, displayed as a waveform or in parametric form, modified with an appropriate graphical input, resynthesized and listened to in quick succession. The disc memory of this system will be compatible with the disc memory of the RAP-1 system (see H-3) so that cartridges can be recorded on the larger system and played-back on the more portable RAP-1 system at the test site.

Assembly of the preliminary system will begin as soon as all of the key elements are available. These are: an 8 channel A/D unit, digital clock, and disc memory (see H-3), and a PC- macromodule interface (see J-13), which are necessary to handle the large quantity of data involved in speech processing.

An important consideration in the system design is the choice of a speech analysis method. A good method should be fast, accurate and suitable for a large variety of different kinds of speech and different talkers. A number of reasonably successful methods have been developed over the past decade. One of these methods, the linear predictor method[1], is being evaluated. The evaluation procedure is to analyze vowel-like waveforms with a known formant structure in order to determine the limits of the analysis method for various conditions of word length, sampling rate, background noise, etc. The vowel-like waveforms are synthesized with cascaded second-order formant resonators excited by an impulse train. It has been found that the formant structure of "whispered" (noise excited) speech can be determined if a large enough sample (10-20 ms) is averaged in calculating the covariance matrix.

A Macromodule setup has also been assembled to experiment with a "real-time" Newton-Raphson algorithm for solving the parameters of the linear predictor speech model. The advantage of this iterative method is that inversion of the covariance matrix is not required. A disadvantage is that the linear predictor parameters are not exactly determined and the resulting error

depends on the rate of convergence of the method. To determine how well this method converges for a wide range of speech will require further study. The number of arithmetic operations are about the same for the iterative method as with the more direct method of inverting the covariance matrix. Further experiments are planned after a multiply macromodule and provisions for sampling and storing large quantities of speech waveforms are available.

(1) B. S. Atal and S. Hanauer, "Speech Analysis and Synthesis by Linear Prediction of the Speech Wave," J. Acoust. Soc. Amer., 50, 637-665, 1971.

H-3. Random Access Programmer for Complex Audio Signals (RAP-1)

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
J. R. Cox, Jr., BCL
J. D. Miller, Ph.D., Central Institute for the Deaf
A. F. Niemoeller, D.Sc., Central Institute for the Deaf
D. A. Ronken, Ph.D., Central Institute for the Deaf
B. F. Spenner, BCL

Support: RR 00396
NS 03856

Because of recent industrial efforts to develop low cost, high capacity disc memories it is now economically feasible to use a disc memory to record and play short sound segments. Such a system for digital storage of complex auditory waveforms has been described (see PR 7, F-15). The advantage of such a system for speech and hearing research over the commonly used magnetic tape recorder is that the experimenter can access different recorded sounds quickly. Random stimulus sequences can be generated without resorting to tedious tape splicing methods. Contingency experimental designs can be used where the stimulus presented depends on previous subject responses.

The disc memory that was originally chosen for the system did not meet manufacturing specifications and has since been replaced with a more suitable disc. This disc offers the added advantages of larger capacity (25 megabits), faster access times, and use of removable cartridges. Cartridges are relatively inexpensive so that each experimenter can have his own cartridge of recorded sounds.

To study various design variables a trial version of the system was built from macromodules using the new disc. Several new devices were developed for use in the trial system and in future macromodular systems. These are: an 8 channel A/D unit, a disc controller, a programmable digital clock, and a TTL-macromodule interface. No serious problems were encountered in interfacing the disc, which operates asynchronously at high data rates, with the input/output

converter stages which operate at a constant, real-time sampling rate. With 8k words of buffer memory it is possible to record and play-back continuously from any combination of track locations on the disc.

It was also determined with the trial system that a sampling rate of 20 kHz and a 12-bit word length would be a suitable compromise between signal bandwidth, quantizing noise and disc capacity in terms of duration of recorded sounds. A sufficiently high sampling rate and word length are necessary since relatively large signal bandwidths and large signal-to-noise ratios are required in many psychoacoustic experiments. For the above conditions 100 seconds of continuous recording can be achieved.

The design of the Random Access Programmer (RAP-1) is essentially complete. All parts have been ordered and construction of the hardware has been started. The RAP-1 system will be a self-contained single-channel recording system. Up to 400 sound segments of duration 250 ms can be recorded, edited, filed, and played-back at random.

The input preamplifier will have a switchable range from 1 mv to 1v rms permitting signals from microphones, record players and tape recorders to be used without the need for additional equipment. A signal-level meter and peak-clipping error light, aid in setting appropriate gain controls. Because of the 12-bit word length and 20 kHz sampling rate, the signal-to-noise ratio and bandwidth of the system will be approximately 72 dB and 10 kHz respectively which is substantially better than existing analog tape recorders.

After a sound segment is recorded into a temporary buffer area on the disc, portions can be edited from the buffer and filed at other locations. An editing window is positioned over the sound segment of interest and the sound within the window can be monitored with earphones and an oscilloscope. Switches are provided on the console to vary the starting point and window length in increments equivalent to 1 ms of the sampled signal.

The RAP-1 system will be mounted in a cabinet on wheels so that it can be moved conveniently between laboratories. Each experimenter will have a cartridge on which he can assemble his own repertoire of complex sounds.

The RAP-1 system will be made to connect to the LINC computer so that more sophisticated forms of editing, filtering, or sound synthesis can be used to make up special sounds. Connections will also be provided so that various subject consoles and control devices can be used to control sound playback during an experiment.

H-4. 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

Recent modifications to the Signal Detection Laboratory Computer System include: retro-fitting the Sykes Cassette Recorder (see PR 7, F-17) and rebuilding the high speed paper tape punch. The Sykes Recorder retro-fit was required to compensate for tape cassette manufacturing variations. The retro-fit consisted of changing the recorders photosensing and read/write circuitry. The paper tape punch was rebuilt to allow the paper punches to be sharpened and realigned.

H-5. A Visual Display of the Helicotrema

Personnel: M. D. Lien, BCL
B. A. Bohne, Ph.D., Otolaryngology
D. H. Eldredge, M.D., Central Institute for the Deaf

Support: RR 00396
NS 03856
Washington University

The perilymph of scala vestibuli in the cochlea is contiguous with that in scala tympani through an opening near the apex known as the helicotrema. Most physical and mathematical models either neglect the helicotrema or assume it to be a simple opening beyond the apical end of the basilar membrane. To a first approximation this simplified description is probably adequate. However, for low frequencies and apical positions along the cochlear model a more complete description of the helicotrema may be necessary to obtain an accurate representation of wave motion for these conditions.

The cochlear duct of the membranous labyrinth is roughly triangular in cross-section with free sides formed by the basilar and Reissner's membranes and with the peripheral side containing the stria vascularis and the spiral ligament closely adherent to the bony labyrinth throughout. The opposite central angle formed at the junction of Reissner's and the basilar membrane is supported by a bony spiral lamina that projects, except near the apex, from the central bony modiolus. At the apex the three walls of the membranous labyrinth converge to end in a blind, bony cup. The bony modiolus ends before the ramp formed by the bony spiral lamina reaches the apex. This leaves a central opening, the helicotrema, surrounded for up to a whole cochlear turn by the bony spiral lamina. The pertinent physical dimensions of the helicotrema are difficult to measure because the opening does not lie in a single

plane and because the opening is bounded by the bony spiral lamina in a manner that keeps the opening from being a complete shunt for pressure differences across the more peripheral and compliant membrane system.

A computer program has been written to generate a three dimensional display of a chinchilla cochlear specimen from histologic sections made parallel to the modiolus. Data points of the histological sections are gathered by rho-theta[1] and transmitted by the PC to the IBM 360 Model 50 for reconstruction. Subsequently these data are displayed on the MMS4 (Molecular Modeling System 4) system of the Computer Systems Laboratory.

Display of the reconstructed sections can be viewed at any angle and depth by simply rotating appropriate knobs on the MMS4. Features of the helicotrema, like its location and size, can be more easily visualized and measured with the help of the three dimensional display. With the aid of this display, more specimens will be studied and the effect of the helicotrema location upon cochlear mechanics will be investigated.

(1) J. R. Cox and J. A. Parker, "Rho-Theta Routines," BCL Monograph No. 55, September, 1970.

H-6. Generalized Waveform Generation

Personnel: M. D. McDonald, BCL

Support: RR 00396

Basic routines were written for the LINC to allow the generation of an almost arbitrarily complex acoustic waveform given the composition of its spectral envelope. Input to the system are the partial number, normalized amplitude, and phase angle for each of a maximum of 85 partials. Output is a 1024 point waveform corresponding in the time domain to a superposition of sinusoids defined by the spectrum. Using these routines, waveforms were generated to demonstrate two well known psycho-acoustic effects.

1. Residue Pitch Effect: A waveform was produced using only harmonic partials ten through fifteen with the fundamental through the ninth harmonic absent. When a tune is played using this waveform, the melody is heard in the octave range of the missing fundamental (128 Hz to 256 Hz) even though the lowest frequency component for which non-zero power is present varies between 1280 Hz and 2560 Hz.

2. Shepard's Effect[1]: Waveforms were generated for each of the twelve tones in a tempered scale, each tone consisting of ten sinusoidal components at octave intervals. The frequency, F, and the power, L, for the Cth component of the Tth tone are given by:

$$F(T,C) = F_{min} \cdot 2^{C-1} \cdot 2^{\frac{T-1}{12}}$$

$$L(T,C) = \frac{22}{56} + \frac{34}{56}\left[1 - \cos\theta(T,C)\right]/2$$

where: $\theta(T,C) = \frac{\pi}{60}\left[12(C-1) + T-1\right]$

$$F_{min} \simeq 5 \text{ Hz}$$

When this series of twelve tones is played repeatedly, each note sounded for 120 ms with exponential rise/decay, and separated from its successor by 840 ms of silence, the effect is of an infinitely ascending (or descending) sequence of tones. Since the jump of an octave in frequency after each sequence of twelve tones is unnoticed, it has been suggested that the common rectilinear scale of measurement of pitch perception is inadequate.

Preliminary design work has begun on a more advanced tone generation system based upon the work of W. Henke[2].

[1] R. N. Shepard, "Circularity in Judgements of Relative Pitch," J. Acoust. Soc. Amer., 36, 2346-2353, December, 1964.

[2] W. Henke, "MITSYN, Multiple Interactive Tone Synthesis System," Research Laboratory of Electronics, M.I.T., November, 1971.

I-1. Internship Program

Personnel: E. L. Morofsky, BCL
R. M. Arthur, Ph.D., Electrical Engineering
J. R. Cox, Jr., BCL
R. R. Pfeiffer, Ph.D., Electrical Engineering
J. T. Zimmerman, BCL

Support: HS 00074

The Health Care Technology Internship Program made its debut during the summer of 1972 with eight participating graduate students of the Biomedical Engineering Program at Washington University. The objectives of the initial six weeks of the program are, 1) to give the students an intimate acquaintance with the workings of various hospital departments and services with an especial emphasis on the effects of recent technological progress, and 2) the isolation of areas where future applications of technical skills will reap the greatest benefits in terms of improved distribution and effectiveness of patient care or increased efficiency of operation. Weekly meetings of the students with the above personnel allow each student to share the experiences of others at locations which he will not visit. The remainder of the summer is devoted to individual projects involving some problem area identified during the initial period and requiring further interaction with a visited facility. It is hoped that some of these projects will be extended into Masters theses. Participating hospitals include Barnes Hospital, Children's Hospital, Jewish Hospital, St. Luke's Hospital, City Hospital of St. Louis, St. John's Hospital, St. Mary's Hospital, Deaconess Hospital and Cochran Veterans Hospital.

I-2. A MUMPS Interpreter for the PC

Personnel: W. E. Long, BCL
J. R. Cox, Jr., BCL
B. F. Spenner, BCL

Support: RR 00396
HS 00074

A version of MUMPS (Massachusetts General Hospital Utility Multi-Programming Systems) has been implemented on the PC. MUMPS has proven in the past to be an effective language for the acquisition, storage, and retrieval of medical record information. One of the original design objectives was to make PC MUMPS directly compatible with a version of MUMPS called MIIS (Meditech Interpretive Information System) offered by Meditech of Cambridge, Massachusetts. MIIS is an enhanced version of MUMPS developed by two of the principle originators of MUMPS. This compatibility has been achieved for the most part. The deviations being due to PC memory constraints and the irrelevance to our system of some of the MIIS commands.

PC MUMPS at present is a single-user system with LINC tape temporarily being used as the mass storage device. The interpreter and operating system take approximately 6.5K of the 8K 12-bit words available. Two versions of the system are available. The first contains a modem interface and is oriented toward the remote user. The second is for the computer console user and contains the necessary I/O drivers to interface with the standard PC display and keyboard.

The system has been designed, coded, and debugged and several monographs have been written[1-3]. The system is being used by application programmers at the present time (see I-3) for the dual purposes of generating viable application programs and field testing the software package.

System timings have been taken in an effort to pinpoint areas where increased efficiency would have the greatest effect on the overall system performance. In order to identify bottlenecks in the system readily, a memory mapping display was designed. Memory was mapped on to an X-Y rectangular graph on the face of a CRT so that each point on the graph would represent a unique memory location. The mapping was accomplished by using the PCs P register to drive the X and Y inputs of the CRT. During operation, subroutines with the heaviest use developed the brightest spots on the display.

A preliminary design study was made to determine the feasibility of implementing these heavily used routines in hardware in an effort to increase the interpreter's overall execution speed. In the coming year these studies will be carried out using macromodules.

The interpreter has been modified to allow software interfacing with devices other than the standard terminal (Datapoint). These include Beehive terminals (with their buffer memory and editing capability) and Repco printers. Implementation of both a fixed head disk and a large (50 megabit) movable head disk are planned for the immediate future. Also, a feasibility study of a multi-user system will be carried out.

A formal course in PC MUMPS is being planned for the fall of 1972 with both BCL and Washington University Medical School students as participants.

(1) W. E. Long, "PC MUMPS - Preliminary Operating Manual", BCL Monograph No. 168, revised July, 1972.

(2) W. E. Long, "PC MUMPS Primer," BCL Monograph No. 171, to be published.

(3) W. E. Long, "PC MUMPS Design Manual," BCL Monograph No. 72, to be published.

I-3. Development of a Patient Encounter Form

Personnel: J. T. Zimmerman, BCL
T. J. Coleman, BCL
W. E. Long, BCL
E. L. Morofsky, BCL
G. T. Perkoff, M.D., Preventive Medicine
M. A. Whitney, Ph.D., Preventive Medicine

Support: HS 00074

A patient encounter form (PEF) is being developed for use in the Medical Care Group (MCG)[1] of Washington University. Through the PEF, we capture the medical care utilization for each patient encounter with a health care provider in the MCG prepaid group practice. Presently, most of the captured data identify the patient, the health provider, presenting complaint, characteristics of services rendered (especially laboratory tests and x-rays ordered), and the next encounter; in the near future we should also include diagnoses and prescriptions. This reporting system is intended to generate cost and utilization data, to provide a foundation for evaluation of the MCG program, and for auditing (quality control of) the medical care provided.

The programs are written in PC MUMPS (see section I-2); and the user interacts with the PC via a video (Datapoint) terminal. The PEF is presented as a series of questions to which the user responds with the appropriate answer numbers. Currently, we are evaluating acceptance by MCG personnel in using, 1) the terminal alone, and 2) the terminal in conjunction with a standard paper-printed sheet listing the appropriate answers and their code numbers. While the latter is expected to be more efficient in terms of the utilization of the time of the user and the computer, the former may be more free of input errors.

Additional programs presently being written include generation from the PEF of 1) summary records of each patient's encounter with MCG; 2) summaries of services provided as a function of health care provider (for quality control); and 3) statistical summaries of service usage as functions of patient age and sex distributions.

[1] G. T. Perkoff and L. Kahn, "The Medical Care Group of Washington University: Development, Goal and Evaluation," University Medical Care Programs: Evaluation, DHEW Publication No. (HSM) 72-3010, 47-54, December, 1971.

I-4. Economic Effects of Technological Innovation in Health Care

Personnel: E. L. Morofsky, BCL
W. F. Pickard, Ph.D., Electrical Engineering
J. T. Zimmerman, BCL

Support: HS 00074
Washington University

Technical progress in the health care system has in the past substantially increased the cost of medical care. The time when technical progress was welcomed without an accompanying estimate of its effects is ended. An impact statement of some sort may well be a future requirement for the introduction of new technology. Proposals might include estimations of the demand for the new or improved service and its effects on cost and quality of care, an explicit statement of the benefits to society versus alternative proposed expenditures, and availability of personnel to maintain and operate the system. The routine filing of such statements would contribute to the task of identifying the most fruitful areas in which health care technology can bring about meaningful reductions in costs, and increased efficiencies of operation and effectiveness of care.

In an effort to prepare our biomedical engineering students to deal with problems of cost overruns, complaints of misplaced expenditures and the general problem of relating engineering analysis to economic contstraints, we plan to devote a significant portion of BMED 549 (Engineering Aspects of Health Care Delivery) to classical engineering economics, cost effectiveness analysis and cost benefit analysis as they interrelate under the general heading of Planning Programming Budgeting (PPB) analysis. It is hoped that PPB will provide the students with a framework in which they may seek financially acceptable solutions to problems confronting health care facilities.

J-1. Kinetics of Chronic Subdural Effusions

Personnel: D. C. DeVivo, M.D., Pediatrics and Neurology
J. Markham, BCL
M. L. Rockoff, Ph.D., Public Health Service

Support: RR 00396
NS 06833

Our efforts in the past year have centered on developing a model to describe the kinetics of the proteins present in the effusion fluid (see PR 7, F-2). Because of the uncertainties concerning the protein movement and the difficulty of obtaining a numerical solution for a complex system, we have been unable to find a model which corresponds to the experimental data previously obtained. We are now analyzing the results of a simplified experiment in an attempt to determine some of the parameters involved. In this experiment a previously studied patient has again been evaluated, now with unbound iodine-125 and iodine-131 administered as sodium iodide. The kinetics of the free radionuclide are being analyzed, hopefully to validate a portion of the theoretical model.

J-2. Lung Inflation and Pulmonary Blood Flow

Personnel: L. J. Thomas, M.D., BCL, Physiology and Biophysics, Anesthesiology
R. W. Hagen, BCL
A. Roos, M.D., Physiology and Biophysics and Anesthesiology

Support: RR 00396
HL 00082
Washington University

Previous studies (PR 6, F-10) of cyclic pulmonary blood flow responses to cyclic lung inflation[1] are being extended to further define this complex interaction. The object of these experiments is to establish the mechanisms for the observed vascular flow responses to changes in lung volume and inflation pressure. Eforts have been directed toward perfecting new techniques and apparatus to measure and control distal bronchial pressure relative to vascular (arterial and venous) pressures during cyclic inflation of perfused lungs in vitro. Distal bronchial pressure is accessed by the method of Macklem and Mead[2] and, as per their findings, is assumed to approximate alveolar pressure. A servo control for a gas flow valve was developed for controlling perfusion pressures relative to bronchial pressure. In addition, a logic circuit was built for adding reversible limit control to a servo controlled piston device for lung inflation with variable amplitude, waveform and frequency.

[1] L. J. Thomas, Jr., A. Roos, D. H. Glaeser, and J. R. Cox, "Pulmonary Blood Flow Response to Cyclic Inflation of Isolated Cat Lungs," Amer. J. Physiol. 221, 808-816, 1971.

(2) P. T. Macklem and J. Mead, "Resistance of Central and Peripheral Airways Measured by a Retrograde Catheter," J. Appl. Physiol. 22, 395, 1967.

J-3. Molecular Model of Cytoplasmic Malate Dehydrogenase from X-ray Diffraction Data

Personnel: L. J. Banaszak, Ph.D., Biochemistry
E. Hill, Ph.D., Biochemistry
L. Webb, Ph.D., Biochemistry

Support: RR 00396
GB-27437X
GM 13925
Washington University

The alpha carbon coordinates of about 700 amino acid residues for the cardiac muscle enzyme, malate dehydrogenase, are now known from single crystal X-ray diffraction data. As described in the previous report (see PR 7, F-26) the analysis of the diffraction data involved teleprocessing with the LINC and the IBM 360 Model 50. The current studies involve more detailed analysis of the electron density maps and the fitting of about 5000 additional atoms into this electron density.

J-4. Correlation of Partial Chemical Sequence Data with Electron Density Maps of Proteins at High Resolution

Personnel: L. Webb, Ph.D., Biochemistry
L. J. Banaszak, Ph.D., Biochemistry
E. Hill, Ph.D., Biochemistry

Support: RR 00396
GB-27437X
GM 13925
Washington University

The final structure of a large protein molecule involves the correlation of amino acid sequence data obtained by chemical studies with the position of atoms obtained from electron density maps. If the amino acid sequence is fully known, this is a relatively simple study. On the other hand if only short pieces of chemical sequence are known, it should be possible to place these short segments in the correct order using the electron density maps. Probability methods for placing these short chemical sequences in the electron density map of the whole molecule are being developed. This method is being specifically applied to malate dehydrogenase but will be of general use for all structural analysis.

J-5. Analysis of the Trabecular Structure of Human Bones

Personnel: R. E. Rider, Ph.D., Physics
S. D. Rockoff, M.D., George Washington University
J. H. Scandrett, Ph.D., Physics
A. R. Zacher, Ph.D., Physics

Support: RR 00396
GM 17386
RR 05389
Washington University

An automatic pattern recognition facility was employed in an experimental study in the analysis of the trabecular structure in bone. This research developed an evaluation method which quantifies the pattern of trabecular shadows on radiographs of the distal radius.

A powerful image processing facility was built utilizing a PDP-11 computer and the IBM 360 Model 50 operated by the Washington University Computing Facilities. The two computers communicate with each other through a shared memory and both have direct access to the image processing hardware. Film is scanned using a random-programmable flying-spot CRT device which has 4096-by-4096 addressing of the x and y axes and which measures 1024 density levels on a logarithmic scale. Visual output displays are generated on a Tektronix 611 storage oscilloscope.

A digital filtering algorithm was developed which uses an 11-by-11 matrix of complex weights. From a weighted sum of densities on the radiograph, line elements of arbitrary angular orientation are detected. The output of the algorithm is invariant to constant and first derivative changes in the input picture density and hence eliminates troublesome sources of background. The algorithm was applied to a mathematical model of trabecular structure so that output quantities could be studied with respect to independent variation in parameters of the model such as length, width, thickness, number and angular distribution of trabeculae. When applied to a 35 mm photocopy of a bone radiograph, the algorithm detects trabecular shadows and is substantially unaffected by cortical thickness or overlying soft tissue.

An automatic procedure was developed for bone radiograph analysis.[1] This procedure was applied to a sample of 100 dried excised human radii and to a twenty-five patient *in vivo* sample. The algorithm produced parameters from dried excised radii which quantified trabecular angular distribution and which correlated with trabecular strength and with the amount of bone mineral. An ordering of the 100 bone sample based on a structure parameter produced by the algorithm showed qualitative agreement with the subjective evaluation of two radiologists. The analysis procedure was applied to *in vivo* radii without modification in a study containing small male and female groups of young, old, and diseased patients. The structural parameters averaged over each group showed systematic differences consistent with known demineralization effects as a function of age, sex, and disease.[2]

(1) S. D. Rockoff, J. H. Scandrett, A. R. Zacher, "Quantitation of Relevant Image Information: Automated Radiographic Bone Trabecular Characterization," Radiology, 101, 435, 1971.

(2) R. E. Rider, "Quantitative Analysis of Trabecular Structure from Human Bone Radiographs," Ph.D. Thesis, Washington University, 1972

J-6. Colony Scanning and Stop-Action Cell Growth Scanning

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

Support: RR 00396
CA 04483

A semi-automatic procedure has been developed which finds all "objects" within a Petri dish but allows human review of the ambiguous cases (overlapped colonies, background noise). Previous attempts at total automation of the colony count have not been completely successful. The procedure automatically counts and sizes the uncontroversial objects of simple shape, then displays the questionable cases for decision by a trained observer. This leads to a substantial reduction in data acquisition time, since a trained technician requires 3-5 minutes to count a dish containing typically 100 colonies, whereas the computer system requires only a few seconds.

A second problem concerns the technique of time-lapse photography for study of individual cell generation cycles and mitosis. Hurwitz and Tolmach(1) using this technique in the study of He La cells, have found that the damaging effects of radiation obey a complicated dynamics. The well-known "mitotic delay" in the first regeneration cycle is followed by a normal regeneration time for the next cycle, followed by a lengthening in the third and fourth generations. The duration of mitosis, typically 5% of the cell cycle, increases proportionally more than the interphase period. The authors suggest that radiation damage occurs through a disturbance of the mitotic process.

Conclusions such as these come from laborious visual scanning of successive film frames and manual recording of individual cell family trees. A simple image analysis method is now under development which shows promise of automatically tracking cells from frame to frame, and determining the occurrence of the mitotic process. We find that a sharply increased ratio, $(\text{circumference})^2/\text{area}$, provides a simple practical signal indicating mitosis.

(1) C. Hurwitz and T. J. Tolmach, "Time Lapse Studies of X-Irradiated He La S3 Cells," Biophysical Journal, 9, 607, 1969.

J-7. A New Mathematical Model for Insulin Production

Personnel: R. Wette, D.Sc., Biostatistics
F. Matschinsky, M.D., Pharmacology
I. N. Katz, Ph.D., Applied Mathematics and Computer Science
E. Rodin, Ph.D., Applied Mathematics and Computer Science

Support: RR 00396
AM 10591
Washington University

Currently, the most widely used mathematical models for representing the dynamics of insulin production in the pancreatic islets are based on compartmental concepts (two compartment model with or without single-threshold conditions). Although the two compartment model appears to be sufficient to describe steady state and some dynamic properties of the system, it breaks down in view of newer experimental evidence. A new model has been developed which integrates major necessary properties disregarded in previous models, such as feedback, and is aimed to be sufficient not only to represent the currently known properties of the system but also to permit its testing by prediction of experimentally verifyable properties not studied so far. The necessary features, suggested from experimental evidence are: (1) The release of insulin from the islets is stimulated by glucose (and/or other chemical agents), and there is a threshold distribution for glucose (and/or other agents) among the islets. (2) The release of insulin is inhibited by insulin, and there is an insulin threshold distribution among the islets. Both thresholds may be correlated. (3) Insulin is stored in inactive form in the islets, released from the stores into intercellular space, where it becomes active, according to the stimulation/inhibition threshold, and the store is replenished independently.

The mathematical description of the model is a system of four non-linear first-order ordinary differential equations with nine arbitrary parameters (diffusion coefficients etc.) presenting an initial value problem. Certain properties (e.g., steady state characteristics) of the model could be found analytically, imposing functional limitations on the form of the threshold distribution. Others, especially regarding the dynamic behavior, are investigated by numerical integration (computer program), using analytical and trial-and-error methods for finding appropriate parameter value vectors. Although the model can represent all known experimentally observed properties of the system in principle, that is to say, that the dynamic and steady state functional characteristics of the system are representable, a linearly proportional fit to observations could not yet be obtained. It is suspected that the major reason for this is the inappropriateness of the threshold distribution used, which assumes threshold-independence, although it is realized that the non-linearities in the system make it extremely difficult to "hit" the correct area in the parameter vector space.

J-8. Numerical Investigation of the Power Function of the Correlated Variance Ratio

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

Support: RR 00396
Washington University

The comparison of two variances by the variance-ratio F-test is inappropriate if the two sample variances are correlated. It could be shown that the F-test is in this case not only not conservative, as previously assumed, but actually invalid in the sense that the size of the test may be too small as well as too large. A modified F-ratio incorporating the correlation coefficient estimate of the variables provides an exact test. The power function of this test is analytically intractable and was computed using a power series approximation. The approximation breaks down for small sample sizes and further work is required to cover this region of practical importance.

J-9. Utility Program Development for Random Pairwise Treatment Allocation

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

Support: RR 00396
Washington University

A production computer program was developed for the pairwise random allocation of patients to two treatments in double or single blind clinical trials. The output format is designed to be used as the allocation protocol.

J-10. Numerical Investigation of the Product Normal Approximation to the Truncated Bivariate Normal

Personnel: R. Wette, D.Sc., Biostatistics

Support: RR 00396
Washington University

In a number of important biomedical applications, such as in human genetics of quantitatively inheritable diseases and in dose-time-response analysis, it is required to evaluate partial integrals of the bivariate normal distribution. Reasonably efficient computer programs to compute these areas appear to be unavailable. A frequently used approach is to approximate the non-normal marginal distribution resulting from single or

double truncation of the bivariate normal by a normal distribution with mean and standard deviation that of the marginal distribution. The goodness of this approximation for evaluating the distribution function was numerically investigated. It was found that the approximation is surprisingly good over a wide range, but may break down in the tails for some areas in the parameter space as defined by the truncation points and the correlation coefficient.

J-11. Stochastic Point Processes

Personnel: D. L. Snyder, BCL

Support: RR 00396
GK-32239

We have found that the theory of stochastic point processes provides a reasonable mathematical model for our studies of both parameter estimation in nuclear medicine (see C-6) and optical communication systems (see E-4). A one semester seminar on this topic was offered in the spring of 1972; there were eighteen attendees, about half of whom were from either PCL or participating in the biomedical engineering program. A set of notes for this course is being written; the first three chapters are now available[1]. Several presentations have been given that deal with point processes[2-7].

[1] D. L. Snyder, "Notes on the Theory and Application of Stochastic Point Processes and Their Application: Chapters I, II, and III," BCL Monograph No. 167, March, 1972.

[2] D. L. Snyder, "Nonrecursive Smoothing for Gaussion Modulated Point Processes," Proc. Ninth Annual Allerton Conference on Circuit and System Theory, 242-245, Sponsored by the E. E. Dept., University of Illinois, Urbana-Champaign, Illinois, October, 1971.

[3] E. V. Hoversten and D. L. Snyder, "On the Performance of Pulse Position Modulation in Direct Detection Optical Communication Systems," Proc. 1972 IEEE International Conference on Information Theory, 8-9, held at Asilomar Conference Grounds, Pacific Grove, Calif., January, 1972.

[4] D. L. Snyder, "An Approximate Nonlinear Filtering Theory for Processing Data Obtained in Nuclear Medicine," Proc. 1972 IEEE International Conference on Information Theory, held at Asilomar Conference Grounds, Pacific Grove, Calif., January, 1972.

[5] D. L. Snyder, "Information Processing for Observed Jump Processes," BCL Monograph 157, September, 1971, Proc. 1972 IEEE International Conference on Information Theory, 63, held at Asilomar Conference Grounds, Pacific Grove, Calif., January, 1972.

(6) D. L. Snyder and I. B. Rhodes, "Filtering and Control Performance Bounds with Implication on Asymptotic Separation," Proc. 5th World Congress, International Federation of Automatic Control, held at UNESCO House, Paris, France, June 12-17, 1972. Also: Control Systems Science and Engineering Report CSSE-735, Washington University, June, 1971.

(7) E. V. Hoversten and D. L. Snyder, "Receiver Processing for Direct-Detection Optical Communication Systems," Proc. International Conference on Communications, Philadelphia, Penn., June, 1972.

J-12. System for Automatic Drug Injection

Personnel: B. F. Spenner, BCL
R. J. Arnzen, BCL
L. J. Tolmach, Ph.D., Radiology
R. N. Tatum, BCL

Support: RR 00396
CA 04483

The system for Automatic Drug Injection (PR 7, F-13) is presently undergoing modifications primarily concerned with the broadcast system. A paper tape reader, which was initially designed to be the source for broadcast information, is being replaced by a dynamic shift register memory. This shift register will provide faster data access and will increase reliability. The modified system will use the paper tape reader to initialize the shift register memory which will then perform the broadcast operation.

Another modification consists of the redesign of the syringe injection system to provide easier access to the syringe drive mechanism.

J-13. An Interface Between Macromodules and the PC-1200

Personnel: P. S. Berger, BCL
J. G. Green, BCL
M. D. Sutton, BCL

Support: RR 00396

An interface to allow the PC-1200 to access macromodules was designed and is presently in the final construction phase. In the manner of similar macromodular interfaces described heretofore(1), the PC/MM interface allows the user to control and perform data manipulation in macromodules by using a special set of input-output commands in the PC software repertoire.

In general, the interface is capable of recognizing the operation to be performed, executing the operation, and providing the necessary translations between non-compatible logic types. In addition to the conventional single-ended control over macromodule operation, an interactive link allows the macromodular system to interrupt normal PC operation and thus allow automatic conditional branching. The user may partition the macromodular completion lines to allow for either type of branching.

The interface is modularly constructed to allow for possible future expansion. In the initial configuration, there are thirty-two macromodule control initiation ports, thirty-two dissociated completion ports, eight buffer registers to provide data to the macromodules and eight data input ports from the macromodules to the PC. Provisions have been made to add six pairs of data ports, thirty-two initiation ports and thirty-two completion ports. The system can be roughly doubled in size.

Other features of the interface are 1)software macromodular presetting capabilities which allow the operator to preset a system under program control, 2)multiple control ports for independent control of two macromodular manifolds and 3)a movable boundary between interrupt-producing completion signals and non-interrupt-producing completion signals.

(1)T. C. Perry, "LINC to Macromodule Interface," CSL Technical Memorandum No. 128, July 30, 1971.

J-14. A Simulation Aid to the Discovery of Oscillitory Behavior in Logic Circuits Under Some Triggering Conditions

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

Support: RR 00396

A software analysis and simulation system has been developed to allow investigation of sequential logic circuits. The specific type of sequential circuits considered were those with feedback yielding the information storage required for synchronization of digital signals. Careful investigation of potential circuits is important since a synchronizer may encounter non-standard input conditions.

The analysis portion of the system identifies the existence of cyclic states which may occur in a sequential logic circuit with feedback. The simulation routine uses the results of the analysis and simulates the

oscillitory behavior of the circuit being examined. The analysis and simulation system is capable of examining sequential circuits consisting of up to ten logic elements.

The system does not provide an exact simulation of a device, but it does furnish a direction for experimentation.

J-15. Design of a Disc Controller

Personnel: N. A. Mullani, BCL
R. L. Hill, BCL
B. F. Spenner, BCL

Support: RR 00396

A general purpose controller has been designed for a class of movable-head disc drives utilizing the IBM 2315 type cartridge (e.g., Diablo Series 30 or Pertec Series 3000). The controller handles the formating of the disc, data transfer and check sum. Some of the features of controller are: 8-bit or 12-bit word length, a variable number of sectors per track, and a variable number of data words per sector. These features enable 8-, 12- and 16-bit computers to have a common data base.

J-16. Arithmetic Routines for the PC

Personnel: J. M. Baker, BCL
M. D. McDonald, BCL
G. C. Oliver, M.D., Medicine
R. S. Rosenfeld, M.D., Medicine

Support: RR 00396
HL 05332

A double precision binary floating point arithmetic package has been written for the PC. This package largely emulates DBLFLT[1] for the LINC. Numbers have ten-bit signed exponents and twenty-one bit signed mantissas. Provision is included for decimal floating point output.

Currently under development is another set of multiple precision floating point routines for the PC, the need for which was dictated by a desire for greater accuracy and flexibility than the above described routines provide. Precision is a minimum of twenty-five bits, using a number format due to W. Simon.[2] The programming approach is modular, so that basic routines may be extracted for use by other PC machine language programs or the entire system may be used as a powerful interpretive arithmetic package.

[1]"DBLFLT," BCL Technical Report No. 2, May, 1967.

[2]W. Simon, "A Scheme for Accelerated Floating Point Operation in Small Computers," Computers and Biomedical Research, 3, 1970.

J-17. Digital Filtering with Macromodules

Personnel: R. N. Tatum, BCL
P. S. Berger, BCL
C. F. Pieper, BCL

Support: RR 00396

A commonly encountered sequence of operations in signal processing is analog preconditioning, sampling, digitizing, and digital conditioning. Analog preconditioning is familiarly thought of in frequency domain concepts, and it is interesting and useful that the other steps in the sequence can be also. The z-transform is the mathematical tool for doing this (as the Laplace transform is in the analog case).

A recursive algorithm is one way to realize a digital filter. For example

$$y(nT) = K_1 y(nT-T) + K_2 y(nT-T) + x(nT) - L_1 x(nT-T) - L_2 x(nT-2T)$$

where x(nT) is the sampled input signal and y(nT) is the sampled filter output. The coefficients K_1, K_2, L_1, and L_2 are filter parameters and T is the sampling interval. The z-domain transfer function of this filter is

$$H(z) = \frac{z^2 - L_1 z - L_2}{z^2 - K_1 z - K_2} = \frac{(z - \alpha_1)\ (z - \alpha_2)}{(z - \beta_1)\ (z - \beta_2)}$$

where α_i and β_i are the z-plane zeros and poles. The frequency response of the filter is determined by the filter parameters.

The algorithm above was implemented with macromodules. Macromodules were chosen because of the ease of construction, the flexibility to modify the algorithm, the high speed of operation, and the convenience of entering parameters. Entering the filter parameters with thumbwheel switches allowed many different responses to be easily realized.

Digitized ECG data was passed through various filters with the goal of improving QRS detection. A notch filter was particularly effective in reducing 60 hertz contamination of data. A possible future application of macromodule filtering may be found in highspeed ECG analysis (see B-5).

VI. TRAINING ACTIVITIES

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

Course in LINC and PC Programming, Fall, 1971

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:

Umit T. Aker, M.D.	Medicine
Jean Y. Barbier, B.S.	Radiology
George L. Bickmore	Computer Systems Laboratory
Mary N. Caston	National Cash Register Company
Teresa P. Germanson, B.A.	Biostatistics
Joseph D. Ferrario, B.S.	Radiology
Joseph G. Green	BCL
Julius Hecht, B.S.	Radiology
Barbara J. Lawrence, M.A.	St. Louis University
Gwenyth A. Loughner, M.S.	BCL
William E. Loughner, M.S.	Medical Library
Michael J. Michno, Jr., Ph.D.	Mechanical and Aerospace Engineering
Virtis E. Moore	Computer Systems Laboratory
David F. Sandel	Computer Systems Laboratory
James K. Scheublein, B.S.	Mechanical and Aerospace Engineering
Robert H. Seale, B.S.	Medical Student
Stephen B. Scharon, B.A.	Asian Studies
Edward M. Wu, Ph.D.	Mechanical and Aerospace Engineering
Craig C. Wier, B.A.	Psychology

Course in LINC and PC Programming, Spring, 1972.

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

Dennis M. Bier, M.D.	Metabolism
William S. Corrie, M.D.	Neurology
Mark H. Jaffe, B.A.	Medical Student
Ben W. Lau	Electrical Engineering
Michael C. Rigden, A.B.	Psychology
Albert J. Tahmoush, M.D.	Neurology
Peter P. Tao, B.S.	Electrical Engineering

Course in Theory of Tracer Kinetics, Spring, 1972

This is a lecture series intended to provide physicians and others active in hemodynamics research with information on the physical and mathematical foundations of tracer kinetics. Special emphasis is placed on those methods which employ external monitoring of radiotracers. Topics covered are: role of theoretical models; differential equations for conservation of tracer mass; stochastic and compartmental models — their uses and limitations; methods of accounting for tracer recirculation; and methods of data processing. The course was given by Kenneth B. Larson. Attending were the following members of the Radiology Department staff:

Mokhtar H. Gado, M.D.
Robert L. Grubb, M.D.
G. Leland Melson, M.D.
Marcus E. Raichle, M.D.
Charles A. Raybaud, M.D.
Robert J. Stanley, M.D.
Bruce W. Weiland, M.S.

Course in Application of Linear Systems Theory to Measurement of Blood Flow by Residue Detection

This is a five day series of lectures and laboratory demonstrations in the use of radioactive tracers in the measurement of blood flow. The course is intended for students in the electrical and biomedical engineering programs. Topics included are: review and motivation for the measurement of blood flow using radiotracers, mathematical models based on linear system theory, review of laboratory procedures for flow measurements in brain, kidney, myocardium, and lung. The course was given by D. L. Snyder (BCL), K. B. Larson (BCL), and R. H. Secker-Walker (Radiology). Those attending were:

Michael Gard, B.S.	Biomedical Engineering Program
Robert Green, B.S.	Biomedical Engineering Program
H. Huang	BCL
William Lang, B.S.	Electrical Engineering
Alan Lipschultz	BCL
Carl Pieper	BCL
George Short, B.S.	Biomedical Engineering Program
Robert Tatum	BCL

VII. SEMINARS

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

"Flow and Diffusion Limitations to Solute Exchanges in the Heart" October 29, 1971	Dr. James B. Bassingthwaighte Department of Physiology Mayo Clinic Rochester, Minnesota
"Indicator — Dilution Studies of Renal Functions" November 11, 1971	Dr. Francis P. Chinard Professor and Chairman Department of Medicine College of Medicine and Dentistry of New Jersey at Newark Newark, New Jersey
"Radiotracer Studies of Venous Stasis: Some Preliminary Results" December 15, 1971	Dr. George W. Roberts Chemical Engineering Department Washington University St. Louis, Missouri
"A Non-Invasive Method for the Absolute Measurement of Regional Cerebral Blood Volume by the Use of X-Ray Fluorescence" February 23, 1972	Dr. Michael E. Phelps Mallinckrodt Institute of Radiology Washington University School of Medicine St. Louis, Missouri
"Why Have Comprehensive Health Planning?" March 31, 1972	Mr. Robert A. Parker Executive Director Alliance for Regional Community Health (ARCH) St. Louis, Missouri
"Maximum Likelihood Estimation of Parameters in Multiexponential Fits to Tracer Data" April 5, 1972	Dr. Tamas Sandor Principal Research Associate Harvard University School of Medicine Boston, Massachusetts

"Some Effects of Technology on the Cost, Quality, Distribution, and Effectiveness of Medical Care" May 11, 1972	Dr. Edward L. Morofsky Postdoctoral Fellow Biomedical Computer Laboratory Washington University School of Medicine St. Louis, Missouri
"Hospital Information Systems I Have Seen — A Coast-to-Coast Epic" May 25, 1972	Dr. Joan Zimmerman Postdoctoral Fellow Biomedical Computer Laboratory Washington University School of Medicine St. Louis, Missouri
"An Evaluation of a Modular Hospital Information System" June 9, 1972	Mr. Homer H. Schmitz Executive Director Management Systems Deaconess Hospital St. Louis, Missouri

VIII. PAPERS, PUBLICATIONS AND ORAL PRESENTATIONS

Arnzen, R. J., "Mechanical and Architectural Considerations in a Design of an Intensive Care Unit," submitted to the 25th Annual Conference on Engineering in Medicine and Biology, Miami, Florida, October, 1972.

Bates, D. J. and Frieden, C., "A System for Computer Analysis of Enzyme Mechanisms," Federation Proceedings, vol. 31, p. 467, 1972.

Blaine, G. J., Cox, J. R. and Pexa, J. M., "A Digital Communication System for Clinical Application," submitted to the 25th Annual Conference on Engineering in Medicine and Biology, Miami, Florida, October, 1972.

Choi, S. C. and Wette, R., "A Test for the Homogeneity of Variances Among Correlated Variables," in press, Biometrics, vol. 28, 1972.

Choi, S. C. and Wette, R., "Tests of Hypotheses on Non-Independent Correlation Coefficients," in press, Biometrische Zeitschrift, vol. 14, 1972.

Cox, J. R., Hagen, R. W. and Thomas, L. J., "Interfacing Physiological Patient Information to a Digital Acquisition System," submitted to the 25th Annual Conference on Engineering in Medicine and Biology, Miami, Florida, October, 1972.

Cox, J. R. and Logue, R. D., "Some Observations on the Economics of Computer Systems for Monitoring Electrocardiographic Rhythms," Computers and Biomedical Research, vol. 4, pp. 447-459, October, 1971.

Cox, J. R. and Nolle, F. M., "Arrhythmia Monitoring Algorithms for Real Time Applications," Proceedings of the Fifth Hawaii International Conference on System Sciences--Computers in Biomedicine, Honolulu, Hawaii, 1972, pp. 120-122.

Cox, J. R., Nolle, F. M. and Arthur, R. M., "Digital Analysis of the Electroencephalogram, the Blood Pressure Wave, and the Electrocardiogram," to be published in IEEE Proceedings.

Elliott, L. L. and Vagely, A. B., "Notes on Clinical Record-Keeping Systems," American Speech and Hearing Association, vol. 13, pp. 444-446, 1971.

Elliott, L. L., Vagely, A. B. and Falvey, N. J., "Description of a Computer-Oriented Record-Keeping System," American Speech and Hearing Association, vol. 13, pp. 435-443, 1971.

Emmerich, D. S., Gray, J. L., Watson, C. S. and Tanis, D. C., "Response Latency, Confidence and ROCs in Auditory Signal Detection," Perception and Psychophysics, vol. 11, pp. 65-72, 1972.

Gengel, R. W. and Watson, C. S., "Temporal Integration: I. Clinical Implications of a Laboratory Study. II. Additional Data from Hearing-Impaired Subjects," Journal of Speech and Hearing Disorders, vol. 36, pp. 213-224, 1971.

Gerth, Jr., V. W., "A Computer-Driven Video Display System for Patient Monitoring," submitted to the 25th Annual Conference on Engineering in Medicine and Biology, Miami, Florida, October, 1972.

Hill, R. L., "Block Coding for Data Compression in Nuclear Medicine," Proceedings of the 1972 IEEE International Symposium on Information Theory, Pacific Grove, California, January, 1972.

Holmes, W. F., "Mass Spectrometer Data Acquisition and Processing Systems," Biochemical Applications of Mass Spectrometry, G. Waller, editor, John Wiley & Sons, Somerset, New Jersey, 1972, pp. 60-61.

Holmes W. F., Holland, W. H. and Parker, J. A., "A Display Oriented Mass Spectrometer-Computer System," Analytical Chemistry, vol. 43, pp. 1806-1811, 1971.

Hoversten, E. and Snyder, D. L., "On the Performance of Pulse Position Modulation in Direct-Detection Optical Communication Systems: Mean-Square Error and Threshold," Proceedings of the 1972 IEEE International Symposium on Information Theory, Pacific Grove, California, January, 1972.

Hoversten, E. and Snyder, D. L., "Receiver Processing for Direct-Detection Optical Communication Systems," Proceedings of the International Conference on Communications, Philadelphia, Pennsylvania, June, 1972.

Larson, K. B. and Snyder, D. L., "A Mathematical Model for Measuring Blood Flow by Residue Detection when Radiotracer Recirculation Interferes," presented at the National Conference on Research Animals in Medicine, Washington, D. C., January, 1972. To be published in the proceedings of this meeting, U. S. Government Printing Office, in press.

Larson, K. B. and Snyder, D. L., "Measurement of Blood Flow by Residue Detection when Recirculation of Tracer Interferes," invited paper presented at the Department of Physiology, St. Louis University School of Medicine, St. Louis, Missouri, March, 1972.

Larson, K. B. and Snyder, D. L., "Measurement of Relative Blood Flow, Transit-Time Distributions and Transport Model Parameters by Residue Detection when Radiotracer Recirculates," in press, Journal of Theoretical Biology.

Larson, K. B., Snyder, D. L. and Metzger, J. M., "Measurement of Blood Flow and Determination of Transport-Model Parameters by External Monitoring of Radiotracers when Recirculation Interferes," presented at the Winter meeting of the American Physical Society, Massachusetts Institute of Technology, Cambridge, Massachusetts, December, 1971.

Larson, K. B., Snyder, D. L. and Eichling, J. O., "Measurement of Blood Flow by External Monitoring of Radiotracers when Recirculation Interferes," Proceedings of the 24th Annual Conference on Engineering in Medicine and Biology, Las Vegas, Nevada, October, 1971, p. 326.

McDonald, M. D., "Methods for Approximating the Logarithm and Exponential Functions for Arguments in Binary Representation," submitted for publication to Communications of the ACM.

Nolle, F. M., "Argus, a Clinical Computer System for Monitoring Electrocardiographic Rhythms," Washington University, St. Louis, Missouri, 1972 (D.Sc. Dissertation).

Nolle, F. M., Ambos, H. D., Clark, K. W., Cox, J. R., Oliver, G. C. and Wolff, G. A., "A Clinical Computer System for Monitoring Electrocardiographic Rhythms," Proceedings of the 24th Annual Conference on Engineering in Medicine and Biology, Las Vegas, Nevada, October, 1971, p. 154.

Oliver, G. C., Cooksey, J., Witte, C. and Witte, M., "Absorption and Transport of Digitoxin in the Dog," Circulation Research, vol. 29, p. 419, 1971.

Oliver, G. C., Nolle, F. M., Tiefenbrunn, A. J. and Clark, K. W., "A Study of the Effect of the Argus Computer System on Treatment Actions in a Coronary Care Unit" (Abstract), The American Journal of Cardiology, vol. 29, p. 284, 1972.

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," Computers and Biomedical Research, vol. 4, pp. 523-541, October, 1971.

Oliver, G. C., Parker, B. M. and Parker, C. W., "Radioimmunoassay for Digoxin: Technique and Clinical Application," American Journal of Medicine, vol. 51, pp. 186-192, August, 1971.

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Roberts, G. W., Larson, K. B. and Spaeth, E. E., "The Interpretation of Mean Transit-Time Measurements for Multiphase Tissue Systems," submitted for publication to the Journal of Theoretical Biology.

Secker-Walker, R. H. and Evens, R. G., "The Clinical Application of Computers in Ventilation-Perfusion Studies," in press, Progress in Nuclear Medicine, 1972.

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Snyder, D. L. and Rhodes, I. B., "Filtering and Control Performance Bounds with Implications on Asymptotic Separation," Proceedings of the Fifth IFAC World Congress, Paris, France, June, 1972, to be published in Automatica, November, 1972.

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