1981

# Progress Report No. 17

Biomedical Computer Laboratory

# PROGRESS REPORT

## No. 17

1 July 1980 — 30 June 1981

**Biomedical Computer Laboratory**

**Washington University School of Medicine**

**700 South Euclid Ave.**

**St. Louis, Missouri 63110**

BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

# PROGRESS REPORT NO. 17

JULY 1, 1980 - JUNE 30, 1981

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# I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes activities during the period from July 1, 1980 through June 30, 1981. The Biomedical Computer Laboratory collaborates with research investigators throughout the Washington University School of Medicine and its affiliated hospitals in the application of advanced computer techniques to problems in biology and medicine. 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 vigorous development and evolution of specialized computer systems for use in the solution of research and clinical problems has continued to be the central focus of BCL activities. Several systems now in clinical use have seen a progression from exploratory pilot studies, to major developmental project, to local clinical trial, to clinical trials in multiple locations, to public availability through commercial manufacture. Perserverance in this sometimes tedious chain of development has found reward in the effective fielding of specialized computer systems to the medical community.

One class of computer applications requires strong coupling of the computer to its environment for digital signal processing. These applications typically involve the use of commercially available minicomputers and microprocessors in conjunction with specialized hardware designed and built locally. We have pursued many such applications by bringing signals from hospital wards and research laboratories to BCL by means of either analog or digital tape recordings or telephone lines and, more frequently, by taking the computers to the investigator's laboratory or the patient's bedside.

For those classes of applications dominated by information processing requirements, provisions have matured from telephone lines linking our minicomputers to the IBM System/360-370 at the Washington University Computing Facilities, through development and support of a minicomputer based MUMPS system, to the establishment of independent groups such as the Medical Computing Facility and the Medical Computing Service Group which serve the local medical complex. Diverse needs continue to be met by these various options while collaborative work continues on more advanced information-processing developments.

Still another 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. Dabeeru C. Rao, and the University Computing Facilities whose director is Robert J. Benson.

The BCL enjoys collaboration with over 15 departmental divisions with the medical school but also finds support and enrichment through close ties with other facilities throughout the University. These arrangements are of benefit both to the BCL and to graduate students who find projects and employment among the activities in the laboratory. The Department of Computer Science is under the direction of Dr. Jerome R. Cox, Jr., past Director of the BCL. Close collaboration with the department currently emphasizes the area of information systems. Strong ties with the Department of Electrical Engineering are sustained through the Engineering School's Biomedical Engineering Program and common interests in digital signal processing techniques. The Department of Electrical Engineering is chaired by Dr. Donald L. Snyder, past Associate Director of BCL.

The Washington University Computer Laboratories is a federation of two research laboratories and two working groups which brings together the interests and resources of major segments of the University. The Biomedical Computer Laboratory is a component of the Medical School. The Computer Systems Laboratory is organizationally directly under the Chancellor. Both BCL and CSL share staff members with the Medical School and the School of Engineering and Applied Science. The Information Systems Group is housed within the Department of Computer Science and the Systems Design Aids Group is housed within the Department of Electrical Engineering.

The Coordinating Committee for the Washington University Computer Laboratories is charged with the task of monitoring long-term interactions between programs. The present composition of the Coordinating Committee is:

J. R. Cox, Jr., (Chairman) Principal Investigator for the Resource and Chairman, Computer Science
C. David Barry, Director, National Collaborative Research Program
R. J. Benson, Director, University Computing Facilities and Assistant Vice Chancellor
S. B. Guze, Vice Chancellor for Medical Affairs
E. L. MacCordy, Associate Vice Chancellor of Research
J. M. McKelvey, Dean, School of Engineering and Applied Science
C. E. Molnar, Director, Computer Systems Laboratory
D. L. Snyder, Chairman, Electrical Engineering
L. J. Thomas, Jr., Director, Biomedical Computer Laboratory
D. F. Wann, Group Leader, System Design Aids

To aid in long-range planning of the health-related activities of the Washington University Computer Laboratories, a National Advisory Panel meets periodically with the Coordinating Committee. Particular attention is given to the confluence of important needs in biology and medicine with the technical advances capable of meeting these needs. Successful developments by WUCL may suggest implementation on a larger, perhaps national scale. The present composition of the National Advisory Panel is:

P. H. Abbrecht, Professor of Physiology and Internal Medicine, Uniform Services University of the Health Sciences, Bethesda, Maryland

H. L. Bleich, Associate Professor of Medicine, Harvard University

W. A. Clark, Consultant and former Director of CSL, Cambridge, Massachusetts

J. N. Gray, Tandem Computer Company, Cupertino, California

F. E. Heart, Bolt, Beranek & Newman, Cambridge, Massachusetts

D. M. Kipnis, Professor and Chairman, Department of Internal Medicine, Washington University

B. W. Matthews, Professor of Physics and Director of the Institute of Molecular Biology, University of Oregon

J. M. Smith, Computer Corporation of America, Cambridge, Massachusetts

E. A. Stead, Jr., Professor of Medicine, Duke University

C. Vallbona, Professor and Chairman, Department of Community Medicine, Baylor College of Medicine

## 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, Division of Research Resources.

RR 00396 A Resource for Biomedical Computing.

A research grant HL 18808, to study the relationship of arrhythmias and sudden death sponsored by the National Heart, Lung and Blood Institute has continued, in collaboration with the Division of Biostatistics and the Jewish Hospital.

A subcontract was continued by the American Heart Association under NHLBI Contract N01 HV 72989 to develop a database for arrhythmia detector evaluation.

Another subcontract was continued by the University of Rochester under NHLBI grant HL 22982 to support establishment of a Multicenter Post-coronary Risk Stratification Program.

NHLBI contract N01 HV 72941 continues to fund a Holter Monitoring Core Laboratory to support a Multicenter Investigation of Limitation of Infarct Size.

Collaborative research continued with St. Louis University, under NHLBI Contract N01 HV 62960, to establish a data management system.

NCHSR grant HS 03792, to develop a medical information systems design methodology, continues to support the research in the Computer Science Department and this Laboratory.

Collaboration with other investigators often involved work already supported by other grants.

Public Health Services grants.

EY 00256 Factors Affecting Intraocular Pressure,

EY 00336 Glaucoma Clinical Research Center,

EY 02044 Automated Digital Processing of the Human Visual Field,

EY 03579 Compliance with Topical (Eye Drops) Ophthalmic Therapy,

GM 28232 Physical Mapping of Yeast Chromosomal DNA,

HD 09998 Clinical Correlations to Vitamin D Status in Infants,

HL 07081 Multi Disciplinary Heart and Vascular Diseases,

HL 13851 Cyclotron Produced Isotopes in Biology and Medicine,

HL 17646 Study of Ischemic Heart Disease,

HL 24394 Clinical Trial of Nifedipine During Cardiac Surgery,

HL 25944 Time-of-Flight Positron Tomograph for Cardiac Imaging,

MH 31054 Mental Health in the Aged: Biomedical Factors,

NS 03856 Auditory Communication and Its Disorders,

NS 06833 An Interdisciplinary Stroke Program,

NS 14834 Mechanisms of Seizures and Anticonvulsant Drugs,

NS 15070 Regeneration and Functional Recovery in Cerebral Cortex.

National Science Foundation Grant.

ENG 76-11565 Information Transmission and Processing for Stochastic Point Processes.

Research support also was received from two industrial collaborators, the American Critical Care, Division of American Hospital Supply Corporation, McGaw Park, Illinois, and from the Pharmaceutical Division of Mead Johnson, Evansville, Indiana.

## III. PERSONNEL

### EMPLOYEES

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

Director

Lewis J. Thomas, Jr., M.D., and Associate Professor of Anesthesiology, Physiology and Biophysics, Biomedical Engineering, and Electrical Engineering

Associate Director

G. James Blaine III, D.Sc., and Affiliate Associate Professor of Electrical Engineering and Computer Science

Senior Research Associates

Jerome R. Cox, Jr., Sc.D., and Chairman and Professor of Computer Science, Electrical Engineering and Biomedical Engineering in Physiology and Biophysics, Senior Research Associate, Computer Systems Laboratory
Harold W. Shipton, C.Eng., and Chairman and Professor of Biomedical Engineering
Donald L. Snyder, Ph.D., Chairman and Professor of Electrical Engineering

Business Manager

Virginia M. Bixon, B.S.

Research Associates

Robert J. Arnzen, Ph.D., and Computer Systems Laboratory
R. Martin Arthur, Ph.D., and Associate Professor of Electrical Engineering
Kenneth W. Clark, M.S.
James G. Dunham, Ph.D., and Assistant Professor of Electrical Engineering
A. Maynard Engebretson, D.Sc., and Central Institute for the Deaf
Ronald W. Hagen, M.S., and Lecturer in Electrical Engineering
Richard E. Hitchens, B.S., and Lecturer in Computer Science
William F. Holmes, Ph.D., and Associate Professor of Biological Chemistry
Kenneth B. Larson, Ph.D.
James G. Miller, Ph.D., and Professor of Physics, and Associate Director for Biomedical Physics, Laboratory for Ultrasonics, and Research Assistant Professor of Medicine

Research Assistants

H. Dieter Ambos, and Instructor in Medicine (Cardiology)
David E. Beecher, M.S., and Lecturer in Computer Science
Gary H. Brandenburger, D.Sc.
Michael W. Browder, M.S.
Wen-Chang Chen, M.A.
Nian C. Cheng, M.S.
Alexander J. Gray, B.S.
Ross K. Hartz, M.S.
Russell E. Hermes, B.S.
Timothy J. Holmes, M.S.
Margaret C. Jost, M.S.
Joanne Markham, M.S.
J. Stevadson Massey, B.S.
M. Michael Maurer, Jr., M.D., and Assistant Professor of Pediatrics
Charles N. Mead, M.D.
J. Philip Miller, A.B., and Assistant Professor of Biostatistics in Preventive Medicine
Patricia Moore, Ph.D.
Stephen M. Moore, B.S.
Jack G. Mottley, M.A.
Kadagattor V. Gurumurthy, M.S., and in Electrical Engineering
David G. Politte, B.S.
Michael A. Province, M.A., and in Biostatistics
Heino R. Pull, B.S.
Kenneth B. Schechtman, Ph.D.
Bert H. Tanaka, B.S.
Kou-Hu Tzou, M.S.

Visiting Research Assistants

Ren Kang Yu
Tian-Ge Zhuang

Engineering Assistants

Stanley R. Phillips
Timothy L. Weadon, B.S.

Technical Assistants

Linda L. Brandenburger, R.N.
Debra A. Butler, R.N.
Jing-Shiang Cheng, M.S.
Diane E. Coffey
Judith D. Compton, R.N.
Ellen M. Friedman, M.S., and in Biostatistics
Kathleen A. Madden, B.A.
Melissa A. Marlo

Mary P. McInnis
Patrick W. McLear
Stephen J. Potter
Steven R. Prothero, B.S.
Chung-Dak Shum
Donald W. Stein, Jr.
Donald A. Terovich, B.A.
Eufaula Thornton
J. Randall Thompson
Stephen G. Turney

Electronic Technicians

Joseph H. Flacke
Deborah A. Proffer
Michael J. Rainey

Librarian

Monica W. Shieh, M.L.S.

Secretaries

Rebecca J. Bozesky
Jill D. Buchholz
Shirley A. Gonzalez-Rubio
Celeste J. O'Rourke
Polly E. Raith

The following members from other departments and divisions have joint appointments with the Biomedical Computer Laboratory to facilitate collaboration and enhance interdisciplinary research:

G. Charles Oliver, M.D., Associate in the Biomedical Computer Laboratory, Professor of Medicine and Chief, Cardiology Division, Jewish Hospital
Rexford L. Hill, III, M.S., Research Associate in the Biomedical Computer Laboratory and Assistant Professor of Computer Applications in Radiology

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

Joseph J. Armistead, B.S.
Steven M. Burns, B.A.
Jerry A. Esrig
Robert O. Gregory, D.Sc., and Professor of Electrical Engineering
Ricardo G. Kortas, M.D.
Creon Levit
Alisa Y. Reynolds
Donald J. Santel
Camile A. Stelzer, M.S.

## 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.

J. Achtenberg, A.B., Medicine
F. Arias, M.D., Ph.D., Obstetrics and Gynecology
G. L. Armstrong, B.S., Electrical Engineering
T. R. Baird, Medicine
W. E. Ball, D.Sc., Computer Science
C. D. Barry, Ph.D., Computer Systems Laboratory
B. Becker, M.D., Ophthalmology
R. J. Benson, J.D., Computing Facilities
L. D. Berenbom, M.D., Medicine
S. R. Bergmann, Ph.D., Medicine
G. E. Bickmore, Radiology
D. R. Biello, M.D., Radiology
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S. B. Boxerman, D.Sc., Health Care Administration and Planning Program
M. M. Buckley, Pediatrics
B. K. Clark, B.S., Cardiothoracic Surgery
R. E. Clark, M.D., Cardiothoracic Surgery
L. A. Coben, M.D., Neurology
P. B. Corr, Ph.D., Medicine and Pharmacology
W. A. Crafford, M.D., Medicine
R. M. Doroghazi, M.D., Medicine
A. A. Ehsani, M.D., Medicine
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E. B. Hagelstein, M.S., Electrical Engineering
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J. L. Roberts, M.D., Pediatrics
R. Roberts, M.D., Medicine
D. L. Rode, Ph.D., Electrical Engineering
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F. U. Rosenberger, D.Sc., Computer Systems Laboratory
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University of Texas Health Science Center, Dallas, Texas

J. T. Willerson, M.D.

University of Vermont College of Medicine, Burlington, Vermont

D. S. Raabe, M.D.

Previous years have seen occasional collaborative efforts with various computer firms and equipment manufacturers. This year projects of joint interest have involved:

Mennen Medical, Clarence, New York and Hewlett-Packard, Waltham, Massachusetts - An arrhythmia monitoring system.

Sandoz-Wander, Inc., Hanover, New Jersey, American Critical Care, Division of American Hospital Supply Corporation, McGaw Park, Illinois, and the Pharmaceutical Division of Mead Johnson, Evansville, Indiana - Collaborative drug studies.

## IV. PHYSICAL RESOURCES

The Biomedical Computer Laboratory (BCL) was formed on April 15, 1964, and the original staff moved into laboratory space at 700 South Euclid Avenue in Saint Louis next to the Washington University School of Medicine's main building complex. While the laboratory has remained at this location, the floor space has increased from the original 5,515 square feet (gross) to the present 18,000 square feet (gross) by renovation and occupation of space in adjacent buildings. Collaborative activities have frequently produced situations in which BCL staff members and systems occupy other areas within the Washington University Medical Center at the site of project applications. Facilities for staff offices, laboratory areas, and computational applications are located within BCL. Also, a machine shop and reference room are shared with a sister laboratory, Computer Systems Laboratory, on the same premises. Other physical resources include a well-stocked electronics shop, a large inventory of electronic and computer test equipment, a variety of digital system modules and both digital and analog recording instruments.

The Laboratory has steadily increased its computing capabilities since the time when a single Laboratory Instrument Computer (LINC) provided the original staff with an opportunity to apply digital computing to a few interesting problems in medicine and biology. The small stored-program LINC computer had been designed specifically for use in biological and medical laboratories where there was a requirement for strong coupling between the computer, the investigator and the experiment. That first LINC is still used for a few service functions at BCL. During the past seventeen years BCL has addressed diverse biomedical problems for which digital computing techniques seemed promising and appropriate, and today BCL has interest and involvement in over one hundred minicomputer systems (representing twenty different makes and models) within the Washington University Medical Center. In addition to these systems, BCL has primary responsibility for resources which include a complement of computing hardware and software from a variety of minicomputer system manufacturers. These resources include: PDP-11's from Digital Equipment Corporation, TI-980's from Texas Instruments Incorporated, PC-12's from Artronix, Inc., 135's from California Data Processors, and MMS-X's developed by the Computer Systems Laboratory.

Access to an IBM 360/370 system at the Washington University Computing Facility and to a MUMPS system at the Medical Computing Facility is available through several data terminals. A printer and terminal are linked to a DEC System 20/40 at the Engineering Computer Laboratory in the School of Engineering. Personal-class microcomputer systems have been incorporated into the design of biomedical research systems and several special-purpose devices have been developed using microprocessor chip-sets and microcomputer board-level assemblies.

# V. RESEARCH PROJECTS

## Introductory Summary

The goal of the Biomedical Computer Laboratory (BCL) is the application of digital computing techniques to problems in medicine and biology. This often requires work in areas stretching from basic physiology through mathematical modeling and frequently to the design of specialized equipment. The Laboratory's capability to respond to a broad range of research needs is the direct result of long-standing BRP support. BCL's research program is organized into several major project areas with the staff grouped into teams whose interests are focused correspondingly.

In the interest of succinctness and to reflect changing emphases in project activities, some organizational changes have been introduced into the Progress Report this year. Projects previously reported under "Systems for Pathophysiologic Studies" and "Central Nervous System Diseases and Electroencephalogram Analysis" are now grouped under a new heading, "Systems for Specialized Biomedical Studies" (Section C). Accordingly, work on regional brain studies employing emission tomography is now reported under "Quantitative Imaging" along with other projects on emission tomography. In addition, a number of the previously separate reports on individual projects have been coalesced where appropriate. As a result of the above changes, this year's Progress Report has been shortened somewhat. A total of 64 research-project reports are now grouped under six areas.

In the area of ischemic heart disease and ECG analysis, algorithm developments for high-speed ECG processing have continued progress toward a major revision of Argus with emphasis on frequency-domain analysis. Work also continues on ST-segment analysis and on approaches to supraventricular dysrhythmia detection even more promising than those previously reported. Two ECG processing systems have full Argus/2H capability and are in heavy use for local, national, and international collaborative studies ranging from fundamental electrophysiology to large-scale clinical trials. A third system based on the IBM system 7 is being discontinued. The American Heart Association database for the evaluation of dysrhythmia detectors is now in the final stage of being readied for distribution. Collaborative studies include two multicenter projects of national scope, a study of sudden death, antidysrhythmic drug evaluations, and an investigation of nifidepine for myocardial protection during cardioplegia. Eighteen institutions from ten cities are involved. Other work is being carried out in collaboration with investigators at Barnes and Jewish Hospitals to study the effects of ischemic injury on myocardial vascular integrity, infarct size modification, electrophysiological and biochemical factors underlying dysrhythmias, autonomic modulation of cardiac potentials, and regional myocardial perfusion and metabolism.

Quantitative imaging embraces fundamental work in tissue characterization via ultrasound and radiation-treatment planning as well as the development and application of positron emission tomography. Tissue interactions with both transmitted and reflected ultrasound are being studied. A geometric acoustics model accounts for reflection, refraction, and defraction and has been coupled with a model of anisotropy. Adaptive beamforming techniques are being developed for quantitative imaging in vivo. Discrimination of normal and infarcted myocardium has been achieved. In the area of radiation-treatment planning, we have validated our method for computing three-dimensional absorbed-dose distributions in inhomogeneous media using differential scatter-air ratios. Work on a practical implementation uses macromodules to capitalize on opportunities for parallelism in the computations and applies the MMS-X system for display of the three-dimensional isodose contours. Work in positron emission tomography now focuses on methods for sub-nanosecond resolution of photon coincidences to allow for the use of time-of-flight data to improve tomographic reconstructions. A nondeterministic algorithm which accounts for time-of-flight uncertainties, fluctuation statistics in annihilation times, and random coincidence events has been developed and is being applied. Emission tomography systems are in use for clinical studies of radio-nuclide uptake by heart, liver and brain.

Systems for specialized biomedical studies include an automated autoradiographic analysis system which has been developed in collaboration with the Departments of Anatomy and Neurology. That system, as originally proposed, is now complete and is undergoing evaluation. Plans now call for upgrading its storage capability to accomodate the archiving of images for retrospective analysis. Work on DNA restriction mapping studies with the Department of Genetics has moved forward with a redesign of the proposed system for automated reading of electrophoretic gels and the development of a probabilistic model for assisting in the design of study protocols. Collaborations with the Department of Ophthalmology include the development of a system for constant-area tonography to study the dynamics of fluid flow in the canal of Schlemm. The tonography system was completed during the past year and is now in routine use. Other collaborations with ophthalmology include the computer-assisted acquisition and analysis of visual field data and the development of a system for chromatic perimetry to study early glaucomatous retinal changes. Other developments include a data acquisition system for extracellular cardiac potentials and a toposcopic display system for electroencephalography.

Databases for disease management and research support collaborations for studies of the natural history of sudden death, the protection of ischemic myocardium, infarct size reduction, ambulatory ECG tape processing, obstetrics, clinical pathophysiology in neonatology, and mineral homeostasis in newborns. The last two are linked and serve as a study system for Information Systems Group work which focuses on the development and implementation of an advanced database system.

Speech and hearing research continues in collaboration with the Central Institute for the Deaf. Work has focused on the development of digital instrumentation for studying alternative sensory modalities for speech

perception, glottal source characteristics, visual clues in lip reading, and the psychoacoustics of speech perception. Recent findings in work on the normalization of speech sounds suggest new directions for theories of vowel perception.

Supporting activities span exploratory biomedical applications, system development aids, and digital hardware and software designs of general utility to other laboratory activities. During the past year, PDP-11 systems have been increasingly prominent in Laboratory projects. The introduction of the RSX-11 system for software support has yielded increased flexibility in the utilization of the Laboratory's computing resources. Communications experiments are directed toward high-speed optical communication with the School of Engineering, some 3.5 kilometers away; and toward the development of a local area network for digital communication throughout the laboratory's building complex. Other work uses locally developed microprocessor-based modules with standardized interconnection (IEEE-488 bus) to serve multiple application needs. Microprocessor development support includes a cross-assembler, an "intelligent console," and a library of system modules.

## Individual Projects

### A. Ischemic Heart Disease and ECG Analysis

The projects reported in this section continue longstanding work in real-time and high-speed ECG analysis. Many of the clinical studies detailed below are natural outgrowths of the ECG analysis work, as are the strong interests in the evaluation of automated arrhythmia detectors. Modeling and signal-processing endeavors in the field of cardiology have taken the form of collaborations which address other aspects of ischemic heart disease, such as the kinetics of enzyme release, myocardial metabolism and blood flow, and the electrophysiologic characterization of abnormal myocardial depolarization. Ultrasonic work applied to myocardial tissue characterization is reported in section B.

A real-time computer-based arrhythmia monitoring system, called Argus, in operation in the Barnes Hospital Coronary Care Unit from 1969-1975, was replaced in 1975 by "Argus/Sentinel," a commercially available version developed through collaboration with the Mennen-Greatbatch Company. The experience garnered with Argus, coupled with an evolving popularity of long-term ECG recordings from ambulant subjects, allowed us, in the early 1970's, to assemble a system, called Argus/H, for the high-speed (60 times real time) processing of those long-term recordings. Argus/H has since processed several thousand recordings for a study of ventricular arrhythmias in survivors of myocardial infarction and several hundred recordings for a host of other studies. Extensive evaluations have verified the integrity of the analysis algorithms, proven the value of the quantified results as compared to conventional manual-scanning techniques, and confirmed the consistency of results on reprocessing.

By the mid-1970's, it was apparent that, although we could continue to use Argus/H, that system, with special-purpose, limited, and expensive hardware, could not support rigorous algorithm development, could not efficiently process the now more-popular dual-channel recordings, and could not meet the demand for the system from the growing volume of recordings resulting from recent interest in therapeutic trials of antiarrhythmic agents and interventions designed to protect the ischemic myocardium. A newer system, called Argus/2H, emerged in 1977 and was duplicated in 1978. The two Argus/2H systems process long-term ECGs for national multicenter clinical studies of interventions to limit infarct size and of post-infarction risk stratification. For such studies, the results of processing are usually saved for subsequent statistical analyses via the University's IBM System/360-370. The systems also provide the power and flexibility necessary for work on algorithm revision and on new signal-processing strategies and they also serve the analysis and documentation needs of other work to generate an annotated digital ECG database for the evaluation of automated arrhythmia detectors. Newer signal-processing strategies employing frequency-domain analysis of the ECG are now bearing fruit, as is a stochastic model for the performance evaluation of event detectors.

A-1. Argus Algorithm Development

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In parallel with extensive applications (A-3) of well-developed ECG analysis programs, continued algorithm development seeks faster and better ways to extract more information from tape-recorded ECGs. Frequency-domain algorithms, reported elsewhere (A-4), are primarily experimental and written in FORTRAN. As such, their computational requirements do not make them particularly efficient for high-speed analysis, however the algorithms do lend themselves to subsequent implementation in specialized hardware. Time-domain algorithms, reported here, focus on QRS detection and classification, supraventricular arrhythmia analysis, ST-segment analysis, pacer-spike detection, and miscellaneous support software programs.

QRS detection and classification. A new QRS detector/delineator has been developed and reported.[1] The effort represented the first step in a major revision of the traditional QRS detection (PRIMITIVE) and QRS classification (CYCLE) stages of Argus. Refinements to the detector and formal implementation were postponed until several improvements in the CYCLE classifier could be implemented. The detection stage relies, to some extent, on a feedback loop from CYCLE in order to use "normal-beat" QQ- and SS-interval information in order to properly delineate incoming beats. A FORTRAN version of CYCLE has been written in order to more easily test changes to that algorithm. The work in supraventricular arrhythmia analysis (vide infra) is expected to contribute to the CYCLE revision. Concurrent with the CYCLE revision is the implementation of an operational version of the new QRS detector.

Supraventricular arrhythmia analysis. Our early work[2] on the detection of supraventricular arrhythmic events had focused on algorithms to characterize each 15-minute period as predominantly "normal sinus rhythm," "sinus arrhythmia," or "atrial fibrillation." Periods of normal sinus rhythm could be further scrutinized to identify SPCs (supraventricular premature complexes). A comparison of the performance of these algorithms against a commercial manual-scanning service showed that the former

approach was superior (PR 16, A-1). However, lack of an adequate database hindered algorithm refinements.

Now, a more substantial database of over 100 tapes with a wide variety of supraventricular phenomena has been accumulated. From these, more than 50 one-hour excerpts, each from a different tape and patient, have been annotated for use in algorithm development. The algorithm now under development is more adaptive to subtle changes in RR intervals, permitting variable criteria under which normally-shaped premature beats may be labeled SPC. The concept of the "characterized 15-minute period" has been discarded. In a preliminary evaluation, the SPC-labeling algorithm was applied to 53 one-hour waveform segments, each from a different randomly selected tape (each tape from a different patient). Total beats numbered 270,613 and included 505 SPCs and 2548 VPCs. Of the 53 records, 23 tapes had no SPCs, 20 tapes had 1-9 SPCs, and 10 tapes had 10 or more SPCs (range 10-167, average 46.7). The overall false-positive rate was less than 1%. The false-negative rate for tapes with at least 10 SPCs averaged 6%; over 90% of these "missed" SPCs failed a conservative prematurity threshold. For the 6 tapes with SPC pairs (14 events) and the 3 tapes with SPC runs (4 events), all events were detected. This evaluation pointed out several weaknesses of the algorithm. Further refinements are underway, and a more-extensive evaluation is planned.

ST-segment analysis. The long-term (Holter) ECG recording offers a unique means to document changing ST segments and thus capture electrocardiologic evidence of myocardial ischemia in the patient's own environment with transitory mental and physical stresses. Nevertheless, providers of automated arrhythmia analysis systems have given little attention to the ST portion of the ECG.

There appear to be at least 2 major reasons for this inattention. First, the largely unanticipated difficulties encountered with arrhythmia analysis and the formidable task of developing evaluation databases have preempted the efforts of most systems developers. Second, there has been little effort to maintain a calibrated ECG signal from patient to recorder to playback device to computer. A calibration pulse sent directly from recorder to tape bears little relationship to the dynamic magnitude of the recorded ECG. Playback of the Holter recording clouds the calibration issue if the operator is allowed to make signal-gain adjustments for purposes of maximizing arrhythmia-detection performance. These practical difficulties preclude the reporting of ST-segment deviations in terms of an absolute millimetric measure at present.

Work has begun at BCL on a method to detect relative changes in ST-segment levels. The methodology expresses ST-segment deviations as percent of QRS height. Such an expression permits detection of real ST changes with or without playback-gain adjustments yet avoids interpretation of signal-gain-induced changes as real. Although expression of ST deviation as percent of QRS height may be a unique approach, the

baseline and ST segment delineation algorithm owes much of its background to concepts provided by the exercise electrocardiologists.[3] Details of our algorithm have been reported elsewhere.[4]

An evaluation of ST-segment measurement strategy was performed using 74 one-hour segments, each from a different tape and patient. The tapes themselves came from commercial scanning firms, multicenter studies, drug studies, and both extramural and local investigators; clinical data and lead-placement information were generally unavailable. The hourly episodes were specifically selected for phenomena which would challenge the ST-segment measurement routine. Such phenomena included large P and T waves, baseline drifts and artifacts, rare and frequent ectopy, high heart rates, wide-QRS conduction defects, W-P-W, and a variety of ST depressions and elevations (including Prinzmetal type). The dataset of 74 was divided randomly, but evenly, into developmental and evaluation sets of 37 each. For more than 7000 30-second frames for which the algorithm measured the ST segment, the overall error rate was about 10% which was contributed by improper baseline (2.8%), J-point early (3.7%), J-point late (2.5%), and late ST (0.9%).

Pacer-spike detection. Some patients in a "clinical trial of nifedipine in cardioplegia" (A-13) require postoperative use of a temporary artificial pacemaker. Dual-channel tape-recorded ECGs obtained from these patients are difficult to analyze with the traditional Argus/2H system which has no means to detect pacer spikes nor to distinguish paced beats from ectopic beats. For more recent recordings, clinical personnel have utilized a lead configuration such that the pacer spikes appear, in one channel, to be much larger than the QRS complex. At least 36 tapes from 15 patients with paced rhythms have been obtained. An algorithm to distinguish paced beats from other ectopic depolarizations is under development. Early results suggest that slope criteria used to make the distinction will vary from patient to patient.

Supporting software. Although the algorithm-development projects described above require substantial programming effort to implement and test concepts, at least an equal amount of effort has been invested in the formulation and rendering of concepts and in the evaluation of implemented algorithms. Too numerous to detail here, these adjunct programs consist primarily of sophisticated graphics routines applied to both video and hard-copy devices.

1. C. N. Mead, K. W. Clark, S. J. Potter, S. M. Moore, and L. J. Thomas, Jr., "Development and Evaluation of a New QRS-Detector/Delineator," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 79CH1462-1C, Geneva, Switzerland, pp. 251-254, September 26-28, 1979.

2. L. J. Thomas, Jr., K. W. Clark, C. N. Mead, and J. W. Mimbs, "Supraventricular Arrhythmias: Strategies for Detection," in Ambulatory ECG Recording, N. K. Wenger, M. B. Mock and I. Ringqvist, eds., Year Book Medical Publishers, Chicago, pp. 213-232, 1981.

3. K. Watanabe, V. Bhargava, and V. Froelicher, "Computer Analysis of the Exercise ECG: A Review," Progress in Cardiovascular Disease, vol. 22, no. 6, pp. 423-446, 1980.

4. K. W. Clark, P. W. McLear, R. G. Kortas, C. N. Mead, and L. J. Thomas, Jr., "Argus/2H Detection of ST-segment Changes in Ambulatory ECG Recordings," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 80CH1606-3, Williamsburg, Virginia, pp. 27-31, October 22-24, 1980.

## A-2. High-Speed ECG Processing Systems Hardware

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Support: RR 00396

Hardware development on the IBM System/7 has been discontinued because of the decision to move Argus development efforts to PDP-11 systems. Therefore, the System/7 configuration has been dismantled and disk and tape peripherals moved to a multi-user PDP-11/34 system (F-2). Efforts are underway to dispose of the System/7 processor.

The Siemens ink jet recorder on the CAL DATA 135 Argus/2H system is being replaced with a Hewlett Packard two-channel annotating recorder. This will also improve software compatability with the other Argus/2H system.

## A-3. Processing of Long-Term ECG Recordings

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In addition to Argus algorithm development (A-1), two Argus/2H systems are heavily used to process long-term (Holter) ECG recordings for a variety of studies. Tape processing protocols have been previously described (PR 15, A-4). Major NIH-sponsored multicenter studies include the ongoing Multicenter Investigation of Infarct Size (MILIS) (A-12) and the recently-concluded Multicenter Post-Infarction Program (MPIP) (A-15). Major ongoing drug studies include an Encainide (Mead-Johnson) study at Jewish Hospital (PR 17, Industrial Collaboration), a Bretylol (American Critical Care) multicenter study (PR 17, Industrial Collaboration), and a clinical trial of nifedipine in cardioplegia (A-13) at Barnes Hospital. To date, total tapes analyzed are 1272 (MILIS), 499 (MPIP), 104 (Encainide), 25 (Bretylol), and 257 (nifedipine).

In order to cope with random arrival times for Holter tapes from not only different studies but from numerous medical centers within some studies, the Holter-tape supervisor utilizes a sophisticated data management system to monitor Holter processing activities and ensure orderly data accumulation (PR 16, D-8).[1]

1. P. Moore, K. W. Clark, K. A. Madden, and L. J. Thomas, Jr., "The Role of a Central Laboratory's Local Data Management System in a Multicenter Study," presented at the Combined First Annual Scientific Sessions Society on Clinical Trials and Seventh Annual Symposium for Coordinating Clinical Trials, Philadelphia, PA, May 5-8, 1980.

## A-4. Frequency-Domain Analysis of the ECG

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During the past three years, we have been exploring frequency-domain analysis of the ECG. Two parameters, the First Spectral Moment (FSM) or center of gravity of the spectrum, and the spectral dispersion (DSM) have proven quite useful as spectral shape descriptors. Both parameters are extracted from a given waveform's amplitude-normalized power spectrum which was chosen because of its waveform-amplitude and fiducial-point independence. Furthermore, all FFT data were generated using the entire PQRST complex rather than limiting analysis to the QRS per se.

We next turned our attention to the more global problem of sorting Normal and Non-Normal waveforms. At present, we are evaluating an algorithm which analyzes and gives a final classification of "Normal" or "Non-Normal" to all beats called "Non-Normal" by Argus/2H. The algorithm consists of two "levels" of sorting logic. First, a beat is labeled as "possibly Normal" if it, when compared to a recent Normal, yields a time-domain correlation coefficient (CC), $r > 0.7$. That threshold is significantly lower than that allowed by stand-alone correlation-coefficient-based algorithms. The "failures" of the first level of beat sorting (i.e. waveforms called "possibly Normal" which in fact are not Normal) are captured by the additional requirement that two of the waveforms' power spectral bands (2-12 Hz and 10-26 Hz) must correlate at $r > 0.9$. The fiducial-point sensitivity of the standard CC is thus "modulated" by the fiducial-point independent (but less specific) power-spectrum CC. Neither parameter alone is sufficient to reliably sort as many waveforms as the two combined. Furthermore, the relative fiducial-point insensitivity of the sorting algorithm makes its use for intermittent processing of the second channel of the ECG recording quite attractive since time-of-occurrence data from one ECG channel may be "mapped" simply into a second channel.

An initial evaluation of 24 10-minute segments from 24 patients has been completed. The Argus false-positive rate was reduced 8-10 fold and the Borderline (narrow Non-Normal) rate decreased 10-30 fold. The latter effect is particularly important for the integrity of supraventricular detection algorithms (A-1) which rely heavily on N-N interval analysis. Finally, there were only two situations out of approximately 5000 beats analyzed in which the algorithm incorrectly classified a waveform as Non-Normal in both channels; there were no instances in which a truly Non-Normal beat was labeled Normal by the algorithm. A more extensive evaluation is currently underway.

## A-5. American Heart Association Database

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HV 72989

Previous reports (PR 16, A-8; PR 15, A-8) have detailed the effort required to assimilate electrocardiographic data from ambulatory ECG recordings for inclusion in a database to be used in developing and testing ventricular arrhythmia detectors. Collection of the necessary data for the database has been completed. Efforts during the past year have been directed toward putting the data in its final form and toward establishing the groundwork for distribution and dissemination of the database.

The database consists of 160 digital tapes. The data on these tapes have been chosen to fit in one of eight possible arrhythmia classes, each class containing twenty tapes. Each tape contains three hours of ECG data of which the last half hour of data has been annotated on a beat-by-beat basis by a panel of expert electrocardiographers.

The twenty tapes in each arrhythmia class are being equally divided into test tapes and developmental tapes. The developmental tapes are to be made freely available to arrhythmia detection system developers whereas the contents of test tapes will be kept confidential so that unbiased evaluations of systems may be made in the future. Division of each class into the two component parts has proven to be time consuming. Every effort is being made to make the test and developmental sets as representative of each other as possible. Members of the database tape-selection committee have been asked to grade each tape on five criteria: 1) ease of QRS identification, 2) QRS feature uniqueness, 3) non-QRS feature uniqueness, 4) a so-called level of trickiness factor, and 5) noise content. Upon review by the four committee members, a composite grading factor is established which is then used to divide the tapes into the two sets. At present, two of the eight classes have gone through this review procedure. The remaining six classes still require a final in-house review before they can be presented for final committee review.

An important step in achieving widespread acceptance of the database was the establishment of a distribution center which would be able to make copies of the database available to users as well as being capable to assist users. A center interested in providing these services was sought and selected. The center chosen was the Emergency Care Research Institute (ECRI) of Plymouth Meeting, PA. A formal arrangement has been established between the ECRI and the American Heart Association whereby the ECRI will distribute the database tapes and, in the future, may be designated the official testing center which will use the database test tapes.

At this time, no database tapes have been made available to the research community, but it is hoped that release of some tapes may be made soon. In the meantime, BCL has made available an example tape to be used by future database users to prepare for the eventual database release. The response to this offer has been overwhelming. We have received nearly thirty requests for this tape in addition to dozens of requests for general information regarding the database. The interest in the database was also very evident at a tutorial presented at the 1980 Computers In Cardiology Conference at which there were over seventy people in attendance representing industry and the research community worldwide.

In the near future we plan to release a large portion of the completed database. An important task to be undertaken is the establishment of a framework by which systems may be evaluated using the test portion of the database. This work will be done in cooperation with the American Heart Association and the ECRI.

## A-6. Performance Evaluation of Ventricular Arrhythmia Detectors

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During the past year we have continued development and refinement of the proposed model (PR 16, A-12) for use in determining performance of ventricular arrhythmia detectors. We introduced a stochastic model based upon estimation-theory techniques which leads to improved estimates of detector performance and makes a step toward insuring independent repeatability of results from evaluation studies. Our model, when compared with present statistical methods, can yield results for sensitivity and specificity which have greater statistical significance for an arbitrary test database. The model also prescribes a consistent and efficient way to make comparisons between ventricular arrhythmia detectors.

Major emphasis has been placed on the refinement of the mathematical derivations of the model equations. We have completed derivation for equations which give us estimated values for the number of correct detections and for the false-negative detection rate for a given detector.

The resulting transcendental equation for finding the correct detection probability is:

$$\frac{J}{\hat{\alpha}} + \sum_j [\psi(c_j + \hat{\alpha}) - \psi(a_j + \hat{\alpha} + 1)] = 0$$

where $J$ is the number of tapes in a test database,

$c_j$ is the number of correct detections on tape $j$,

$a_j$ is the number of annotated events on tape $j$, and

$\hat{\alpha}$ is the maximum-likelihood estimator for determining the estimate of the detection probability $\hat{p}$ where $\hat{p} = \frac{\hat{\alpha}}{\hat{\alpha} + 1}$.

Likewise, we have derived a transcendental equation for finding an estimate of the false detection rate. The equation is given as

$$\frac{J}{\hat{\beta}} - \sum_j \left[ \frac{(f_j + 1)}{t_j(1 + \frac{\hat{\beta}}{t_j})} \right] = 0$$

where $J$ is the number of tapes in a test database,

$f_j$ is the number of false detections on tape $j$,

$t_j$ is the length of tape $j$, and

$\hat{\beta}$ is the maximum-likelihood estimator for determining the estimate of the false detection rate which is simply $1/\hat{\beta}$.

The existing model seems to give better estimates of detector performance than methods currently used. However, before any final conclusions are drawn, we must validate several assumptions made during development of the model. The availability of the American Heart Association Database (A-5) will provide us with a database for use in the validation of the model. Further development of the model will include establishing bounds on the variance of the estimation error. These bounds will depend upon many of the model parameters and should give an indication of the amount of data needed to effectively utilize the model. Successful application of the model for determining performance of ventricular arrhythmia detectors should then allow us to pursue application of similar modeling techniques to other types of automated detection systems.

A-7. Assessment of Vascular Integrity of the Myocardium Following Ischemic Injury

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Support: RR 00396
HL 07081
HL 17646
The Kilo Diabetes and Vascular Research Foundation

We have continued our previously reported studies (PR 15, A-10; PR 16, A-10) of the pathophysiology of ischemic injury to the heart. During the past year we have been able to characterize further the time-dependent effects of ischemic injury on membrane-permeability characteristics of the cardiac vasculature. In addition to studies of alterations of myocardial integrity brought on by ischemia, we have developed an experimental model for vascular injury that uses colloidal silica in order to induce endothelial-cell damage. Our emphasis has been on the development and application of a two-compartment model for analysis of data obtained by external detection of radiation emitted by iodine-125 used to label bovine-serum albumin ($^{125}$I-BSA) during washout of the tracer from isolated perfused rabbit hearts subjected to these manipulations. The mathematical model we have applied, which describes transport of tracer by convection and diffusion, is comprised of vascular and interstitial compartments separated by a permeable membrane. Resistance to diffusive transport of the tracer is assumed to arise predominantly in the barrier separating the two compartments; this barrier is identified in the model with the capillary endothelium.

In our experiments, radiolabeled tracer is administered as a bolus and the detector response is fitted to the parameterized function

$$r(t) = A_1 e^{-\alpha_1 t} + A_2 e^{-\alpha_2 t}.$$

In the above, t denotes elapsed time after bolus administration; r(t), the radioactivity counting rate registered by the external detector at time, t. The A's and $\alpha$'s represent model parameters related to the physiological parameters of perfusate flow, F, compartment volumes, $V_1$ and $V_2$, and membrane permeability-surface-area product, PS. A maximum-likelihood method of parameter estimation for radiotracer kinetic data, developed some years ago at BCL,[1] was implemented and applied in order to obtain estimates of the various parameters. Data obtained from control

hearts and hearts subjected to 30 and 60 minutes ischemia were evaluated with this technique. Preliminary evidence indicated that estimates of PS for $^{125}$I-BSA increased significantly from baseline values during reperfusion, from $(3.01 \pm 0.80) \times 10^{-3}$ ml $sec^{-1}$ $g^{-1}$ to $(15.69 \pm 5.44) \times 10^{-3}$ ml $sec^{-1}$ $g^{-1}$. Similarly, estimates of the parameter combination $PS/V_1$ also increased significantly during reperfusion following ischemic injury, from a mean baseline value of $(3.21 \pm 0.46) \times 10^{-3}$ $sec^{-1}$ to $(13.80 \pm 5.72) \times 10^{-3}$ $sec^{-1}$. Although the latter result could be attributed to a decrease in $V_1$, this conclusion seems unlikely because estimates of the model parameter combination, $F/V_1$, representing the convective rate of tracer egress from the coronary vasculature, were not significantly increased over baseline values following ischemic injury. This suggests that neither capillary collapse nor altered perfusion pressure (F was maintained constant) were significant factors. In view of the fact that contractility of hearts subjected to 30 minutes of ischemia returned to baseline values during reperfusion, these results suggest that the coronary vasculature may be more sensitive than the musculature to ischemic injury.

Colloidal silica, which was extensively dialyzed and filtered through 300,000-MWCO Amicon filters before use, was utilized for disruption of endothelial membrane integrity. Preliminary evidence indicated that reperfusion following silica treatment resulted in significant increases in albumin mean-transit time, as well as changes in BSA permeability within endothelium. These observations closely parallel results obtained during reperfusion following 30 minutes of ischemia and provide further evidence of endothelial susceptibility to injury.

1. J. Markham, D. L. Snyder, and J. R. Cox, Jr., "A Numerical Implementation of the Maximum-Likelihood Method of Parameter Estimation for Tracer-Kinetic Data," Mathematical Biosciences, vol. 28, pp. 275-300, 1976.

A-8. Modification of Infarct Size

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Studies were performed in the Cardiac Care Unit at Barnes Hospital to assess the effects of selected pharmacological agents on infarct size, ventricular dysrhythmia, and hemodynamics in patients with mycardial infarction. Infarct size was estimated from serial plasma creatine kinase (CK) changes during a 72-hour interval and results in controls were compared to those observed in the treated group. All Holter tapes were digitized and processed by the Argus/H computer system. Hemodynamics including cardiac output were determined by the Swan-Ganz thermodilution technique and the effects of drugs were assessed by comparing hemodynamics before and after administration. In selected cases, left ventricular function was assessed by radionuclide ventriculograms before and after therapy.

We have previously shown that patients with anterior and inferior infarctions have similar infarct sizes but that the mortality in patients with anterior is 23% compared to only 11% in patients with inferior infarctions. The patients with inferior infarctions exhibited more impairment of right ventricular function reflected by hemodynamics and less left ventricular impairment compared to patients with anterior infarctions with similar infarct sizes. Thus, we postulated that inferior myocardial infarction is more frequently associated with right ventricular damage than is generally appreciated and that the hemodynamic impact of the same overall infarct size is shared by both ventricles. In contrast, in patients with anterior infarctions the impact is felt by only the left ventricle. This hypothesis may in part account for why patients with inferior infarctions have a better long-term prognosis. To further test the hypothesis, studies were initiated with radioventriculography to assess regional ventricular wall motion in right and left ventricles of patients with anterior and inferior infarctions. All patients admitted to the clinical investigation unit had $^{99m}$Tc-red blood cell ventriculograms

performed. Global and inferior and lateral regional right ventricular and left ventricular ejection fractions were measured. Studies have progressed well and to date 180 patients have entered into the study. In controls, right ventricular ejection fraction averaged 43 ± 9% (SD) with variability in repeat studies of 7%. Regional ejection fractions averaged 85 and 65% in inferior and lateral zones. Right ventricular ejection fraction was depressed early after anterior myocardial infarction (28 ± 11) but returned to normal within 10 days (43 ± 12, $p < .001$). Inferior and lateral regional right ventricular ejection fraction exhibited comparable sequential changes (Inferior = 30 ± 13 and 21 ± 11; Lateral = 28 ± 9 and 36 ± 6). In contrast, after inferior myocardial infarction, right ventricular ejection fraction depression, evident at 48 hours (23 ± 9), persisted (28 ± 9 and 32 ± 2 at 10 and 90 days respectively) and correlated with enzymatically estimated infarct size ($r = .85$). Regional inferior and lateral values were comparably and persistently depressed. Thus, global and regional right ventricular ejection fraction are depressed only transiently after anterior infarction but are persistently depressed after inferior myocardial infarction, suggesting concomitant right ventricular injury.

A prospective study was initiated in September 1979 involving all patients admitted to the Coronary Care Unit with documented myocardial infarction. The study was designed to determine and characterize the incidence and nature of early recurrent myocardial infarction (extension) based not only on clinical and electrocardiographic criteria but also on analysis of plasma MB CK, plasma myoglobin and serial radioventriculograms and to identify features of patients at particularly high risk. Patients following transfer from the Coronary Care Unit were continuously monitored by telemetry for a total of at least 14 days. Clinical and electrocardiographic status were monitored and recorded at least daily throughout the hospitalization. Serial plasma samples were obtained for assay of total CK, MB CK, and myoglobin every 4 hours for the first 72 hours and every 12 hours subsequently for 14 days. Re-elevation of MB CK activity to > 15 IU/l after decline of values to baseline or < 8 IU/l were considered evidence of recurrent necrosis. Serial radionuclide ventriculograms were initially performed within 2 days and repeated within 12 days after the onset of initial symptoms. Following is a brief summary of the results obtained in the initial group of 200 patients enrolled, which served as the training set to determine if certain characteristics would permit prediction of patients at high risk of developing early recurrent infarction.

Among the 200 patients studied (128 males, 62 females) mean age averaged 68 ± 17 years. Initial infarction was transmural in 62%, subendocardial in 29% and of undetermined locus in 9%. The overall hospital mortality was 14%; 15% among patients with transmural and 12% among patients with subendocardial myocardial infarction. The 165 patients (83%) without early recurrence had an overall hospital mortality of 13.4%; 17.7% for patients with transmural but only 7% for patients with subendocardial infarction. Among the 35 patients (17%) who experienced early recurrent infarction, for those following an initial transmural infarction there was an overall hospital mortality of 25% compared to

16% in patients with an initial subendocardial infarction. Thus, the patients with initial subendocardial and recurrent infarction had an increase in mortality of 128% (16% versus 7%) over that of patients with subendocardial myocardial infarction; 25 (43%) exhibited early recurrent infarction compared to only 8% of those with initial transmural mycardial infarction. Thus, 71% of all recurrences were seen in patients with an initial subendocardial infarction.

To improve the discrimination of those patients at high risk of developing recurrent infarction beyond that obtained from consideration of locus of infarction alone, associations between subsequent recurrent myocardial infarction and ten dichotomous and two continuous variables were examined. Stepwise logistic analysis yielded four significant descriptors (subendocardial locus, recurrent pain, female gender and obesity) with an overall discriminating power of 80%. The study was continued and 134 new patients were enrolled and followed for recurrent infarction. Utilizing the previous 200 patients as a training set to obtain the regression coefficients for the four descriptors, the new set of patients were analyzed prospectively to test their predictive value to identify patients with early recurrent infarction. The presence or absence of early recurrent infarction was predicted correctly in 82% of patients (23/28) who developed it and 79% who did not (84/106). Thus, four readily available clinical parameters exhibit remarkable predictive power (80% level) discriminating between patients who will and those who will not develop early recurrent infarction. Such predictive power permits selection of a subset of patients at high risk for recurrent infarction in whom it is particularly suitable to assess the efficacy of prophylactic interventions.

A-9. Electrophysiological and Biochemical Factors Underlying the Genesis of Dysrhythmias Due to Myocardial Ischemia and Infarction

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Support: RR 00396
HL 17646
AHA 81-108

The focus of these studies is the correlation of electrophysiological derangements and biochemical and adrenergic neural factors underlying malignant dysrhythmia due to ischemia. The overall concept of the research is that potential arrhythmogenic metabolites accumulate in ischemic tissue and exert deleterious effects on membranes and that their effects may be exacerbated by the concomitant influences of the adrenergic nervous system. Thus, the research involves the interaction between potential arrhythmogenic metabolites within ischemic tissue and the influence of adrenergic neural influences on the generation of these metabolites and their overall impact on the profound electrophysiological sequelae apparent in ischemic tissue in vivo. During the last several years, we have demonstrated that disparate electrophysiological alterations underlie those dysrhythmias induced by ischemia alone compared to those dysrhythmias induced by reperfusion of the coronary artery. Since both types of dysrhythmias may be collectively important in sudden death in man, each may require different therapeutic interventions. In addition, studies have been completed demonstrating a major electrophysiological role of α-adrenergic stimulation during both coronary occlusion and reperfusion.[1] Thus, it appears that during both coronary occlusion alone, as well as during subsequent reperfusion, enhanced electrophysiological responsivity occurs to α-adrenergic input and is associated with the induction and the persistence of malignant ventricular dysrhythmia.

More recently, we have completed a series of experiments to assess whether the enhanced α-responsivity characteristic of ischemic tissue was associated with a corresponding increase in α-adrenergic receptors assessed using $^{3}$H-prazosin.[2] Within 30 minutes after occlusion, total α-receptor number ($\beta_{max}$) in ischemic regions increased to 178% of control values (to 27 $\pm$ 4 fmole/mg protein, $p < .001$). This increase persisted during early reperfusion but values returned to control 15 minutes after reperfusion (13 $\pm$ 1.6). The affinity constant, $K_D$ (2.4 $\pm$ .2), from Scatchard analysis, was not significantly altered at any time. Beta-receptor number ($^{3}$H-DHA binding) and $Na^{+}$-$K^{+}$ ATPase activity in control and ischemic myocardium 30 minutes after occlusion and 2 minutes after reperfusion were not altered. Thus, the enhanced α-adrenergic responsiveness and

marked antiarrhythmic effectiveness of α-adrenergic blockade during ischemia appears to be mediated through a reversible increase in available $\alpha_1$-adrenergic receptors. The time course of increase in $\alpha_1$-adrenergic receptor number correlates with enhanced electrophysiological responsivity and suggests that one promising approach to the treatment of malignant ventricular dysrhythmias during myocardial ischemia may be blockade of α-adrenergic mediated influences. Recent preliminary findings indicate that α-adrenergic blockade with phentolamine completely attenuates the two-fold increase in $Ca^{+2}$ accumulation seen in reperfused myocardium. Currently, studies are being performed: 1) to determine whether reperfusion of the ischemic myocardium is associated with an increase in the identifiable vascular space measured with $^{3}H$-inulin; 2) to determine whether α-adrenergic blockade alters this apparent change in vascular space and whether this would account for the lack of change in $Ca^{+2}$ accumulation during reperfusion; 3) to ascertain whether isolated myocytes, after exposure to elevated $K^{+}$ (12 mM) and/or lysophosphoglycerides to simulate conditions during ischemia in vivo develop an α-mediated increase in calcium uptake using $^{45}Ca^{+2}$; and 4) to determine which mechanisms might be involved in the increased α-adrenergic receptors during ischemia including changes in membrane phospholipids, membrane fluidity and pH.

As reported in PR 16 (A-15) we have detected the accumulation of lysophosphoglycerides in ischemic myocardium early after myocardial ischemia as well as in effluents from isolated perfused hearts under hypoxic conditions.[3] Studies in vitro in isolated Purkinje fibers and ventricular muscle have indicated that lysophosphatidyl choline (LPC) induces marked electrophysiological alterations closely analogous to those changes characteristic of ischemic tissue in vivo,[4] implicating this amphiphilic metabolite as one potential biochemical mediator of malignant dysrhythmia associated with ischemia. More recently, we have demonstrated that LPC increases two-fold in effluents from ischemic feline myocardium in vivo within 10 minutes of coronary occlusion.[5] This two-fold increase in LPC in effluents, coupled with acidosis typical of that seen in ischemic regions in vivo (pH = 6.7) is sufficient to induce marked electrophysiological derangements and may explain the arrhythmogenic properties of venous effluents from ischemic zones.[5] Additional studies have demonstrated that the arrhythmogenic effects of LPC increase 3-fold in the presence of concomitant acidosis.[6] Thus, the concomitant effects of acidosis and accumulation of arrhythmogenic metabolites such as lysophosphoglycerides may be a primary progenitor of the ventricular dysrhythmias associated with early ischemia. Our initial findings demonstrating increased LPC and LPE in ischemic myocardium were spuriously elevated due to intrapreparative conversion of myocardial plasmalogens to lysophosphoglycerides verified by $^{31}P$-NMR.[7] More recently, we have demonstrated using chloroform:methanol extraction procedures with phospholipid separation by isocratic HPLC that the tissue concentration of LPC plus LPE increases 53% during 10 minutes of ischemia in vivo to 7.5 $\pm$ 3 nmol/mg protein and that comparable concentrations induce dramatic electrophysiological derangements in vitro.[8]

Long-chain acyl carnitine also accumulates in ischemic tissue in vivo, particularly in the presence of elevated free fatty acid (FFA) and shows striking structural similarities to LPC.[6] Long-chain acyl carnitine (L-palmitoyl carnitine) induces electrophysiological alterations in canine Purkinje fibers analogous to those seen with LPC. In addition, as with LPC, the effects of palmitoyl carnitine were exacerbated by acidosis; the effects of palmitoyl carnitine were also additive to that of LPC.[6] Thus, acyl carnitine accumulating during ischemia, coupled with concomitant acidosis and the presence of arrhythmogenic effects of the LPC together contribute to the amphiphilic burden of the heart and may be a major precipitant of malignant ventricular dysrhythmia.

More recently, studies have been completed to determine whether alterations in transmembrane potentials induced by LPC depend on actual incorporation of LPC into the membrane assessed by electron microscopic autoradiography (EMA). In these studies,[9] canine Purkinje fibers or ventricular muscle studied with standard microelectrode procedures were incubated with $^{14}$C-palmitoyl LPC under conditions of normal or reduced pH. After 10 minutes, a portion of the tissue was rapidly removed from the bath, washed, and extracted for lipid analysis with chloroform: methanol; the remaining tissue segment was superfused without LPC until electrophysiological recovery and then extracted for lipid analysis. Lipids were separated by HPLC and individual $^{14}$C-phospholipids quantified by scintillation spectrometry. In Purkinje fibers, changes in maximum diastolic potential, amplitude and $V_{max}$ occurred only when LPC incorporation was greater than or equal to 0.62 nmol/mg protein. Average incorporation was 1.1 $\pm$ .13 nmol/mg representing 2.2 $\pm$ 0.2% of membrane phospholipids totaling 50 nmol/mg protein. The major cellular component which was labeled was the sarcolemma, as assessed by EMA. In ventricular muscle at the time of maximal electrophysiological alterations, $^{14}$C-LPC incorporation was slightly higher (1.62 $\pm$ .28 nmol/mg protein) than that in Purkinje fibers, although this represented only 1% of total cellular phospholipid (160 nmol/mg protein).[9] During recovery, $^{14}$C-LPC content decreased significantly with corresponding increases in $^{14}$C-phosphatidyl choline (PC) and $^{14}$C-FFA. Thus, despite increases in PC and FFA during recovery, electrophysiological parameters returned to control values. Although acidosis augmented the electrophysiological derangements induced by LPC, there was no increase in apparent incorporation during treatment or regional metabolism of $^{14}$C-LPC during recovery under acidic conditions.[9]

To determine whether the electrophysiological alterations induced by LPC in vitro resulted in action potentials dependent exclusively on the slow inward current ($I_{si}$), LPC effects were examined in superfused canine Purkinje fibers with inhibitors of fast (tetrodotoxin) and slow (verapamil or $Mn^{+2}$) channels.[8] As reported in PR 16 (A-15), LPC induced action potentials dependent exclusively on $I_{si}$ is exquisitely sensitive to acidosis and thus under conditions of ischemia with concomitant LPC and acidosis, action potentials dependent exclusively on $I_{si}$ may not be initiated. In an extensive series of experiments, we demonstrated that slow-response action potentials were propagated despite the presence

of concomitant acidosis (pH = 6.7) in both canine Purkinje fibers and ventricular muscle.[8] In addition, slow response action potentials induced by increasing extracellular potassium to 22 mM and addition of isoproterenol were also not blocked by concomitant acidosis in either ventricular muscle or Purkinje fibers. Thus, LPC can induce action potentials dependent exclusively on $I_{si}$ in both ventricular muscle and Purkinje fibers, independent of concomitant acidosis, suggesting that in the milieu of ischemia action potentials dependent exclusively on $I_{si}$ may propagate reentrant circuits, thereby exacerbating malignant ventricular dysrhythmia.


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## A-10. Research Projects Utilizing the Isolated-Probe Data Acquisition System

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Support: HL 13851
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The research in this project is designed to noninvasively characterize myocardial perfusion with radiotracers labeled with positron-emitting isotopes. Studies are conducted in isolated perfused rabbit hearts (perfused with media containing washed sheep erythrocytes) to permit control of many factors that modify myocardial perfusion and metabolism in vivo. Studies are also performed in intact dogs using a newly developed beta probe in order to characterize tracer kinetics in vivo. Both preparations are designed to provide definitive information needed for optional implementation of approaches of proven value in positron-emission tomography.

The development of valid, quantitative, noninvasive measurements of myocardial metabolism in man is dependent on the thorough characterization of the behavior of fatty acid in cardiac tissue. Since palmitate is the fatty acid used primarily by the heart, we are currently characterizing the myocardial kinetics of $^{11}$C-palmitate. In isolated hearts, tracer time-activity curves obtained by coincident detection of the positron emission utilizing the isolated-probe data-acquisition system are recorded with simultaneous measurement of a number of myocardial and metabolic functions. In this manner, $^{11}$C-palmitate washout curves can be quantitatively analyzed and parameters compared to chemical determinations. Myocardial time-activity curves, monitored for 20 minutes after aortic injection of 50 μCi of albumin-bound $^{11}$C-palmitate exhibit 3 distinct monoexponential phases, the first representing vascular transit. The

second phase, occurring 2-7 minutes after injection has been correlated by invasive analysis with the $^{14}C$-analog to be primarily affected by fatty-acid oxidation. The third monoexponential phase, occurring 10 minutes after bolus injection, represents activity residing primarily in the triglyceride fraction of myocardial lipids. In studies completed during the past year, residual fraction (the amount of tracer remaining in the myocardium after bolus administration) and turnover rate constants of the resulting monoexponential phases were shown to be altered at constant flow by the administration of $4.1 \times 10^{-7}$ M epinephrine, an intervention known to increase cardiac work and increase lipolysis. After administration of epinephrine, the residual fraction of the second phase was increased, although the turnover time was not affected, indicating that a greater fraction of fatty acid participates in beta oxidation, an effect that is known to occur with epinephrine. In addition, the residual fraction in the third phase was not altered while turnover time was significantly decreased, indicating increased triglyceride utilization. In another series of experiments completed within the past year, hearts were subjected to perfusion with alpha-bromopalmitate, a fatty acid analog known to inhibit fatty acid metabolism. Although myocardial function was not altered, fatty acid utilization was diminished by > 60%. Analysis of the myocardial time-activity curves after a bolus injection of $^{11}C$-palmitate demonstrated decreased extraction of fatty acid by the heart indicating inhibition of oxidation. Thus, changes in fatty acid metabolism were readily detectable externally with $^{11}C$-palmitate.

In a related study in intact dogs, the time-activity curve after a bolus injection of $^{11}C$-palmitate into the left-anterior-descending coronary artery obtained with a newly constructed beta-probe, was observed to closely resemble curves obtained from isolated perfused hearts. Curves obtained from dogs demonstrate three monoexponential phases. Perfusion of the left-anterior-descending coronary artery with hypoxic blood rather than arterial blood at a constant flow rate led to a decrease in clearance of $^{11}C$-palmitate of greater than 70%, indicating that the decreased clearance of $^{11}C$-palmitate after hypoxia is a consequence of impaired aerobic metabolism. The results of these studies indicate that $^{11}C$-palmitate should be useful in studying noninvasively fatty acid alterations induced in the myocardium in a variety of cardiac diseases known to alter fatty acid metabolism, as long as delivery (perfusion) is not limiting.

In related studies, the quantitative dependence of myocardial extraction and clearance of $^{201}Tl$ was characterized in isolated perfused hearts. When flow was decreased, residual fraction and clearance were increased. Conversely, the residual fraction increased and clearance was shortened when flow was increased by 60%. Both residual fraction and clearance remain constant with hypoxic perfusion and with increased work. Thus, although altered work and oxygenation do not affect myocardial thallium kinetics, myocardial extraction increases and clearance is less rapid with decreased flow. Accordingly, thallium scintigraphy, used clinically to detect ischemia, underestimates the severity of ischemia.

The results to date in isolated perfused hearts and intact, open-chest dogs have facilitated interpretation of analogous studies performed in intact dogs studied with positron-emission tomography with both metabolic ($^{11}$C-palmitate) and perfusion ($^{11}$C-butanol and $^{82}$Rb) tracers. These studies indicate that sequential tomography with $^{11}$C-palmitate localizes and detects myocardium with metabolism compromised by transitory ischemia, and that accurate assessment of myocardial perfusion can be obtained utilizing $^{11}$C-butanol. Further studies are planned to characterize the biochemical fate of $^{11}$C-palmitate after alterations induced with metabolic and pharmacological interventions. In addition, studies are in progress to characterize the relative influences of metabolism and perfusion on the kinetics of $^{11}$C-palmitate.

## A-11. Interactive Digital Acquisition of Electrocardiograms

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Support: RR 00396
Washington University

The development of a microprocessor-based (Intel 8080) cart to perform interactive acquisition of ECGs was previously described (PR 16, A-18). This 8-channel system permits collection of all the signals in either the standard 12-lead or the Frank lead systems simultaneously, while testing for signal quality. It contains a 3-channel, strip-chart recorder for waveform output and a self-scan display for presentation of alphanumeric messages to the operator. The operator enters demographic data on the subject and controls the processing sequence through a 16-character keyboard.

The ECG cart was used to study the extension of structured-design techniques now in use for software development to encompass microprocessor-based instrumentation in which the hardware and software aspects of the system are intimately coupled. To accomplish this extension, the concept of mapping, i.e. the creation of outputs from inputs to a processing activity was broadened to include the logical description of the necessary hardware components. In a structured software system these mappings are provided by an operating system in response to read or write commands. In a microprocessor-based instrument these mappings must be built around both software routines and hardware peripherals. In such a hybrid system it is much simpler and more convenient to use the same tools to design and describe both hardware and software than to rely entirely on circuit diagrams and program listings.

There are three phases to the methodology which emerged from this study. The first was termed Operational Requirements and included basic planning and definition of all processing tasks within the instrument. The second was the Implementation phase. It included logical and physical design, system construction and programming, and installation. The final phase was documentation of the operating characteristics of the instrument.

There are two primary advantages of this methodology. First, the design is well-structured on paper, thus expediting corrections during construction. Second, a change in the technology of a given hardware subsystem causes minimal downtime and ideally no disruption to other subsystems. Similarly, the effects of a change in or addition of a subroutine is understood before any reprogramming is begun so that software modifications can be performed efficiently.

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## A-12. Multicenter Investigation of Limitation of Infarct Size (MILIS)

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On August 1, 1978 Washington University, in collaboration with four other centers implemented phase II of the collaborative clinical

trial of therapy to protect ischemic myocardium. The overall goals of the project include objective evaluation of the efficacy of administration of hyaluronidase and of propranolol in limiting the extent of infarction among patients with acute myocardial infarction and in modifying prognosis. Data are being acquired from five clinical centers, including Washington University, Massachusetts General Hospital, The Medical Center Hospital of Vermont, Parkland Hospital in Dallas, and the Peter Bent Brigham Hospital in Boston. Each of the clinical units is enrolling patients to provide an overall sample size sufficiently large to test the hypotheses being explored.

In addition to the five clinical units participating in the study, a series of core laboratories is utilized so that uniform objective analyses of data obtained from each unit can be performed in a blinded fashion. These core facilities include a CK Reference Laboratory (at Washington University), a Holter Recording Analysis Reference Laboratory (also at Washington University), an Electrocardiographic Reference Laboratory (at the Peter Bent Brigham Hospital), a Myocardial Infarct Scintigraphy Laboratory (at Parkland Memorial Hospital in Dallas), a Radionuclide Ventricular Function Laboratory (at the Massachusetts General Hospital), and a Pathology Core (at Duke University). Data from each core laboratory are forwarded to a Data Coordinating Center (Research Triangle Institute; North Carolina) so that objectivity in data management and statistical analyses can be assured.

The Washington University components of this project comprise the Clinical Investigation Unit, directed by the Clinical Unit Coordinator, Dr. Allan S. Jaffe, the CK Reference Laboratory, directed by Dr. Robert Roberts, and the Holter Core Reference Laboratory, directed by Dr. Lewis J. Thomas, Jr.

The final protocol, developed after 18 months of planning, defines studies among patients with suspected myocardial infarction identified as early as possible after arrival at each clinical unit and specifically within 18 hours of the onset of acute symptoms leading to admission. The diagnosis of infarction is based on electrocardiographic criteria, clinical indices, and confirmed with the use of isoenzymatic criteria. Patients to be excluded are those with cardiogenic shock, 75 years of age or older, and those with other significant illnesses or conditions that may affect their response to therapy. Therapy comprising either administration of placebo, propranolol, or hyaluronidase is administered in a randomized fashion. For purposes of randomization, patients are initially divided into two groups based on the presence or absence of possible contraindications to propranolol. Management of patients participating in the study is standardized by a regimen developed during the planning phases to provide maximum safety to the patient and to avoid potentially conflicting effects of other unnecessary medications. Medical management of each patient remains the responsibility of his own personal physician and adjunctive emergency measures are, of course, instituted whenever indicated.

A series of endpoints is being utilized to assess the effects of therapy on the extent of infarction and on prognosis. These include enzymatic estimation of infarct size based on analysis of serial changes in plasma MB and total creatine kinase activity,[1] the extent of infarction assessed from the number of electrocardiographic leads in which initial ST-segment elevation is followed by development of criteria of transmural infarction, the distribution and extent of impairment of ventricular function assessed from radionuclide ventriculograms, the severity and persistence of ventricular as well as supraventricular[2] dysrhythmias assessed from Holter recordings. Additional endpoints include exercise tolerance tests six months after the episode of infarction, $^{99m}$Tc-pyrophosphate scintigrams as well as clinical follow-up recorded on standardized forms developed during the planning phases of the project. Radioventriculograms are obtained three months after infarction, along with a 24-hour Holter recording. Six months after infarction, myocardial infarct scintigrams are obtained along with a repeat 35-lead precordial electrographic map and 24-hour Holter recording. A Pathology Core performs studies among patients who expire during the acute or follow-up phases of the study for whom autopsy permission can be obtained.

Since the Clinical Unit began operations in August of 1978, there have been 3,056 patients admitted to the Coronary Care Unit. During that period 1,415 patients (46%) have been screened for participation in the MILIS protocol. One hundred and twenty-two patients have been enrolled. Since the initial difficulties with MILIS recruitment during 1978 and early 1979, enrollment has been maintained at the proposed level of 50 patients per year. During the twelve months from March 1, 1980 through February 28, 1981, fifty-one patients were randomized. Of these, 43% received therapy within 8 hours of the onset of symptoms. Ten of these patients (20%) were found not to have acute myocardial infarction on the basis of local analysis of plasma MB CK and were discontinued from the protocol after 72 hours.

The studies continue to be of high quality with more than 90% of the MILIS end-point data having been accomplished. Despite frequent malfunctions of the QRS-map acquisition cart (Instruments For Cardiac Research (ICR)) and the need for frequent use of the back-up system, few electrocardiographic studies have been lost. Of the possible zero- and 90-minute studies only one zero-time study and one 90-minute study were inadequate due to equipment malfunction. These studies were obtained but were not adequately recorded. Since the printing function of the ICR cart was non-operative, it was not possible to know that this problem had occurred. Five additional studies were missed at 72 hours and 1 patient died prior to the 72-hour study. In three of these instances patients refused and in another a patient who was deemed too ill by the Clinical Unit Director died shortly thereafter on the same day. In only one instance was there a Clinical Unit failure in the 72-hour studies.

During the interval between March 1, 1980, and January 31, 1981, all follow-up activities were performed in accordance with the MILIS protocol. The activities included 32 three-month follow-up visits,

38 six-month follow-up visits and 68 contacts for subsequent health status forms. Ninety-eight percent of all patient contacts (138/141) were made. However, 7 of 360 testing procedures were not performed due to the patients' health (2%) and 25 of 260 were not performed due to patient refusal (7%). Overall, 91.9% of all end-point data required during the follow-up interval by the protocol were obtained and forwarded to the appropriate Core facilities.


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## A-13. Clinical Trials of Nifedipine in Cardioplegia

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Support: RR 00396
HL 17646
HL 24394


This project involves computer analyses of 24-hour Holter tapes obtained preoperatively and serially postoperatively for the first 72 hours, at 7 days, and 6 to 9 weeks after surgery. The purpose is to study the effects of different methods of myocardial preservation during cardiac surgery. There are two categories of patients: those that receive cardioplegic solution alone or those that receive the same solution containing nifedipine. The rationale is that use of the calcium antagonist will decrease the ingress of calcium ion during the ischemic and immediate reperfusion time intervals, thus improving myocardial recovery. Prior laboratory data have demonstrated that hearts treated with nifedipine in cardioplegic solution have better left ventricular performance in the post-ischemic phase than do those treated with cardioplegic solution alone.

The clinical protocol utilizes radionuclide ventriculograms, pyrophosphate scans, CK-isoenzyme MB, and 24-hour Holter monitoring. Additionally, intra- and post-operative evaluations of hemodynamics are performed. During the initial 12 months of the study there have been 17 patients treated with cardioplegic solution alone and 30 treated with nifedipine in cardioplegia.

The Holter recordings were obtained with Avionics two-channel recorders and the tapes were analyzed using the Argus/2H arrhythmia analysis system and a highly trained editor. The data were reported in tabular and histographic hourly form and included total PVCs, total PVCs corrected for data loss, peak hourly PVC rate, hourly PVC rate corrected for data loss, number of runs of 3 or more sequential PVCs, number of couplets, and presence of bigeminy. Using these data, an attempt was made to compare arrhythmia rates in both groups of patients. Preoperatively, the groups appeared to be similar. Analysis of 42 tapes showed similar PVC rates of $44 \pm 33$ and $47 \pm 18$, respectively. Postoperatively, when only those that were not paced for the first three postoperative days were considered, there were eight control patients and 13 nifedipine-treated patients. There was a marked difference in PVC rates. The control group showed average hourly rates of 5, 15, 15, and 19 for the preoperative, operative day and first two postoperative days respectively. Corresponding average hourly PVC rates for the nifedipine-treated group (N=13) were 63, 39, 67, and 44.

Five of sixteen patients (31%) in the control group required pacing at the end of operation while five of 26 (19%) in the treated group needed pacing. During the initial 72-hour postoperative interval, 31% of the control patients and 29% of the nifedipine treated patients required pacing during at least one 24 hour interval.

The Argus/2H arrhythmia analysis system can not distinguish between a PVC and a paced beat. Consequently, the second channel of the recorder is now used to record paced beats directly from the pacemaker generator as an interim measure. Paced beats are ignored and intrinsic beats are analyzed. A new program which recognizes paced beats is under development and when fully tested will be used for the remainder of the study. The preliminary results noted above are still inconclusive regarding the effects of the intervention on dysrhythmias, but they do underscore the importance of developing the capability to analyze accurately the recordings taken during periods of intermittant pacing.

A-14. Natural History Study of Sudden Death

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Support: RR 00396
HL 18808
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The grant for this study was terminated in the past year. As reported in PR 16, A-7, a total of 2175 patients have been studied. Since last year, several studies have been published or accepted for presentation at national meetings. A study of in-hospital mortality comparing first inferior and anterior transmural infarctions demonstrated a significantly lower mortality for inferior infarctions. When the infarcts were stratified according to size estimated by peak enzyme elevation, a significant difference in mortality persisted. This is compatible with the hypothesis that some of the enzyme elevation seen with acute inferior infarction derives from the right ventricle and has little influence on morbidity and mortality which is more dependent on left ventricular function. This study is in contrast to our previously reported data on non-transmural and transmural infarcts where control for infarct size estimated by peak enzyme reduced to non-significant differences in mortality.[1]

We have looked at various features of PVCs found during Holter monitoring of patients recovering from acute myocardial infarction. An exciting finding is that PVCs of different coupling intervals may respond differently to antiarrhythmic therapy. For example, quinidine therapy may abolish short-cycle PVCs, couplets and runs without affecting total PVC rates.[2]

One very interesting and potentially important finding relates to the significance of late PVCs with coupling intervals > 600 ms. on Holter tapes. These beats are found in high association with runs of either ventricular tachycardia or A.I.V.R. and, relative to their incidences, induce repetitive ventricular activity more frequently than PVCs with coupling intervals between 400-600 ms. We are actively studying their effect on mortality.[3]

Another report has demonstrated that the three-year mortality of first non-transmural vs. transmural infarcts is essentially the same (approximately 20%), but the time curve of mortality is significantly

different. A higher mortality for transmural infarcts is seen in the first year and conversely a significantly higher mortality for non-transmural infarcts occurs between the second and third years. The variables predicting mortality in the first year are not the same as those predicting mortality later.[4]

Another study related the clinical features recorded during acute infarction with the development of ventricular runs in the first year after infarction. Runs in the first three months were strongly related to peak enzyme levels and indices of left ventricular function. These variables still had an effect on late runs recorded from four to 12 months post infarction, but the influence was weaker. The best predictor of runs in the late period was runs in the first three months. The patient group with the highest risk of runs also had the highest mortality, but this increase in mortality was not accounted for by an increase in sudden death.[5]


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2. R. J. Krone, J. P. Miller, R. E. Kleiger, K. W. Clark, and G. C. Oliver, "The Effectiveness of Antiarrhythmic Agents on Early Cycle PVCs," Circulation, vol. 63 pp. 664-669, 1981.

3. R. E. Kleiger, S. Thanavaro, J. P. Miller, M. A. Province, E. Friedman, and G. C. Oliver, "Late Premature Ventricular Complexes; A Marker of Complex Ventricular Ectopic Activity," to be presented at the 47th Annual Scientific Assembly of the American College of Chest Physicians, San Francisco, October, 1981.

4. R. J. Krone, E. Friedman, S. Thanavaro, J. P. Miller, R. E. Kleiger, and G. C. Oliver, "Long Term Prognosis of Patients with First Transmural and Nontransmural Myocardial Infarction," Circulation, vol. 62, p. III-39, 1980 (abstract).

5. R. E. Kleiger, J. P. Miller, S. Thanavaro, T. F. Martin, M. A. Province, and G. C. Oliver, "Relationship Between Clinical Features of Acute Myocardial Infarction and Ventricular Runs Two Weeks to One Year Following Infarction," Circulation, vol. 63, pp. 64-70, 1981.

A-15. Multicenter Post-Infarction Program

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The purpose of the Multicenter Post-Infarction Program (MPIP) has been previously described in Progress reports PR 15, A-19 and PR 16, A-19.

The totals for eligible and recruited patients as well as the percentages of patients undergoing each of the tests for the two St. Louis centers, Jewish Hospital and St. Luke's are summarized below.

| | Jewish Hospital | St. Luke's | St. Louis Total |
|---|---|---|---|
| Eligible Myocardial Infarctions | 160 | 57 | 217 |
| Enrolled | 91 | 35 | 126 |
| % Enrolled | 56.88 | 61.40 | 58.06 |
| % Holter Recording | 100.00 | 100.00 | 100.00 |
| # Holter Recording | 91 | 35 | 126 |
| % Radionuclide Ventriculograms | 89.01 | 94.29 | 90.47 |
| # Radionuclide Ventriculograms | 81 | 33 | 114 |
| % Activity Exercise Test | 54.95 | 45.71 | 54.38 |
| # Activity Exercise Test | 50 | 16 | 66 |
| % All 3 Tests | 52.75 | 45.71 | 50.79 |
| # All 3 Tests | 48 | 16 | 64 |

The total number of tapes analyzed by BCL and reviewed by cardiologists was 499.

A study to compare the two computer systems at Columbia University (CU) and at Washington University (WU) used to process the MPIP Holter tapes has been performed and reported.[1] Eighteen tapes were re-read at CU, 21 tapes at WU, and 46 tapes were cross read. Compared variables included record length (LOR), data loss (DL), ventricular ectopic depolarization count (VEDC), and VED rate (VPH), as well as VED forms (VEDF), R on T, and repetitive VED. Analysis showed good agreement for most

of these variables in the repeat reading although the CU repeat reading tended to have higher VEDC and VPH. Although LOR and DL differed significantly in the cross reads between WU and CU, reflecting different protocols, the key variables of VEDC and VPH showed high correlation in the cross-read group. VEDF also showed acceptably high correlation between the two processing centers as well as in re-reads at each individual center.

1. K. W. Clark, L. M. Rolnitzky, J. P. Miller, J. J. DeCamilla, R. E. Kleiger, S. Thanavaro, J. T. Bigger, Jr., and other MPIP participants, "Ambulatory ECG Analysis Shared by Two Independent Computer Labs in the Multicenter Post-Infarction Program (MPIP)," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 80CH1606-3, Williamsburg, Virginia, pp. 271-274, October 22-24, 1980.

B. Quantitative Imaging

Although ultrasound has proven to be a useful source of diagnostic information, results of examinations based on current ultrasonic methods are primarily qualitative and pictorial. To provide quantitative information in addition to a picture, a collaborative effort with the Department of Physics and Cardiology has continued to address tissue characterization via ultrasound. Quantitative images have been made at BCL for several years using transmitted ultrasound with a multiple-frequency attenuation and time-of-flight tomographic reconstruction system which was used this year to study anisotropy of attenuation in heart and liver (B-3). Temperature regulation and filtering of fluid in the scanning ank have been improved (B-1). Improvements also were made in the software used to simulate ultrasonic transmission and tomographic reconstruction (B-2). Quantitative imaging with reflected ultrasound received added emphasis. Performance of linear phased arrays was characterized via simulation (B-4). Hardware was built to steer and focus the transmitted beam from a linear array, and a maximum-likelihood estimator for attenuation coefficient in the presence of random scatterers was derived (B-5).

Work accomplished during the past year in developing accurate procedures based on fundamental physical principles for computing absorbed dose in clinical radiation-treatment planning is described in this section. Algorithms based on the computation, in three dimensions, of the intensity of Compton scatter and absorption within an inhomogeneous irradiated region have been implemented with special-purpose hardware (B-6, B-7). The speeds achieved thereby, together with the progress made in developing appropriate displays of the computed results (B-8), suggest that our goal of developing a clinically useful tool can now be realized.

Stimulated by the clinical impact of the EMI transmission tomographic scanner in 1973, experimental studies were initiated in collaboration with the Division of Radiation Sciences to evaluate the positron coincidence-detection as a method for emission reconstruction tomography. This collaborative activity resulted in a prototype scanner called PETT (Positron-Emission Transaxial Tomograph). Extensive studies in patients and animals were conducted with the PETT III scanner in collaboration with the divisions of Neurology and Cardiology. A subsequent scanner, PETT IV, utilized concepts developed with its predecessor but incorporated a novel technique for the simultaneous collection of four tomographic slices from a single set of detectors. PETT IV is now located in the Cardiac Care Unit for use in the SCOR project for the quantification of regions of myocardial ischemia and infarction (B-9, B-10). Subsequent scanners have been developed that permit more rapid data collection and improved spatial resolution. One of these, PETT V, was used in experimental studies in dog hearts. The newest system, PETT VI, became operational during the summer of 1980 and employs new, fast detectors and an entirely circular motion for rapid data acquisition. Further development of PETT VI and some experimental studies occurred over this past year (B-11, B-12, B-13). One of the most exciting recent possibilities for emission tomography results because of new developments in crystal technology and high-speed electronics. These now permit the propagation time of each of the two photons created in an annihilation to be measured. Theoretical and experimental studies have been initiated so that a new scanner collecting and using these time-of-flight measurements can be built (B-14 through B-19).

## B-1. Ultrasonic Attenuation and Time-of-Flight Tomographic Scanning System

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J. G. Miller, BCL
D. W. Stein, Jr., BCL

Support: RR 00396

The mechanical scanning portion of the tomographic imaging system[1] (PR 16, B-1) has been improved by the incorporation of a better temperature regulating mechanism and a new fluid. The improvements consist of the addition of a separate ballast reservoir of temperature-controlled fluid. This fluid is continuously pumped into the scanning tank using a diatom filter (Vortex Products) for cleaning, with return flow accomplished by a passive siphon. This system regulates temperatures to within $\pm$ 0.2 deg C during scanning procedures.

The digital acquisition and processing systems currently are being re-evaluated as a consequence of the impending changeover from the PC 1200 processor to a recently acquired LSI 11/23. With the incorporation of an array processor anticipated for the coming year, this change will provide a reduction of about two orders of magnitude in processing time for tomographic images.

1. J. R. Klepper, G. H. Brandenburger, J. W. Mimbs, B. E. Sobel, and J. G. Miller, "Application of Phase-Insensitive Detection and Frequency-Dependent Measurements to Computed Ultrasonic Attenuation Tomography," IEEE Transactions on Biomedical Engineering, vol. BME-28, no. 2, pp. 186-201, February 1981.

## B-2. Modeling and Simulation of Ultrasound Propagation via Geometric Ray Tracing

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J. G. Mottley, BCL

Support: RR 00396
Washington University

Work has continued on the development of an ultrasound wave propagation simulation system (PR 16, B-3). Here we give a description of the system, followed by two examples of simulations compared to experimental data obtained from well-characterized test objects.[1]

A. Ray-Tracing-Based Simulation Methods

Figure 1 illustrates the organization of the simulator. Descriptions of both the intervening medium (the iso-index regions) and the transmitted beam geometry serve as input to the ray-tracing portion of the simulator. To maximize the generality and usefulness of data resulting from the time-consuming ray-tracing step only the minimum information required to trace a beam (its geometry) is employed in the tracing phase. Remaining beam information is withheld until the later ray-summing portion of the simulation. Typically, many different beams, from various transducers over different frequency ranges, may share the same ray geometry. Thus, from a single ray-tracing the effects of many different beams may be studied simply by running the ray-summing portion of the simulator with different beam descriptions. The specific input data to the ray-tracing algorithm are:

1) the iso-index model of the intervening medium (boundary, refractive index, mass density, and frequency-dependent attenuation associated with each iso-index region);

2) the launch angles and spacings of the rays at the transmitting aperture;

3) the distances from the center of scanner rotation to the transmitter and receiver; and

4) the tomographic scan specifications (number of angular views, angular increment, number of translation samples and the sample distance).

The ray-tracing portion of the simulator produces a pseudo-tomographic scan file. Associated with each scanner position is a set of time-of-flight and attenuation measurements, each sampled at discrete ultrasonic frequencies. Unlike a conventional scan file, however, each measurement has associated with it up to 100 rays of information; each ray possesses a termination-position in the receiver plane, a relative intensity, and a time-of-flight. Remaining details about the specific transmitted beam are taken into account at ray-summing. Ray intensities are scaled and the time-of-flight values are adjusted according to the model for the particular transmitted beam.

The ray-summing algorithm for computing the measurement corresponding to the set of up to 100 rays must take into account: a) the type of receiving transducer employed (piezoelectric or acoustoelectric); b) analog or digital filtering employed prior to detection; c) the method of detection (i.e. method for estimating the incident amplitude or intensity from the electrical response); d) the transmitted waveform. In experimental studies of tomography at this laboratory, attenuation was measured as a function of frequency by transmitting narrowband gated-sinusoidal bursts.[2] For both piezoelectric (PE) and acoustoelectric (AE) receiving transducers, conventional gated peak-voltage detection methods often are employed. In this study, envelope-peak detection was employed for the PE transducer. However, an alternative method was employed for the AE receiver. The AE pulse was first low-pass filtered to remove any residual piezoelectric response, then applied to a gated analog integrator. The output of the integrator, sampled after an appropriate interval, is proportional to the total incident acoustic energy.

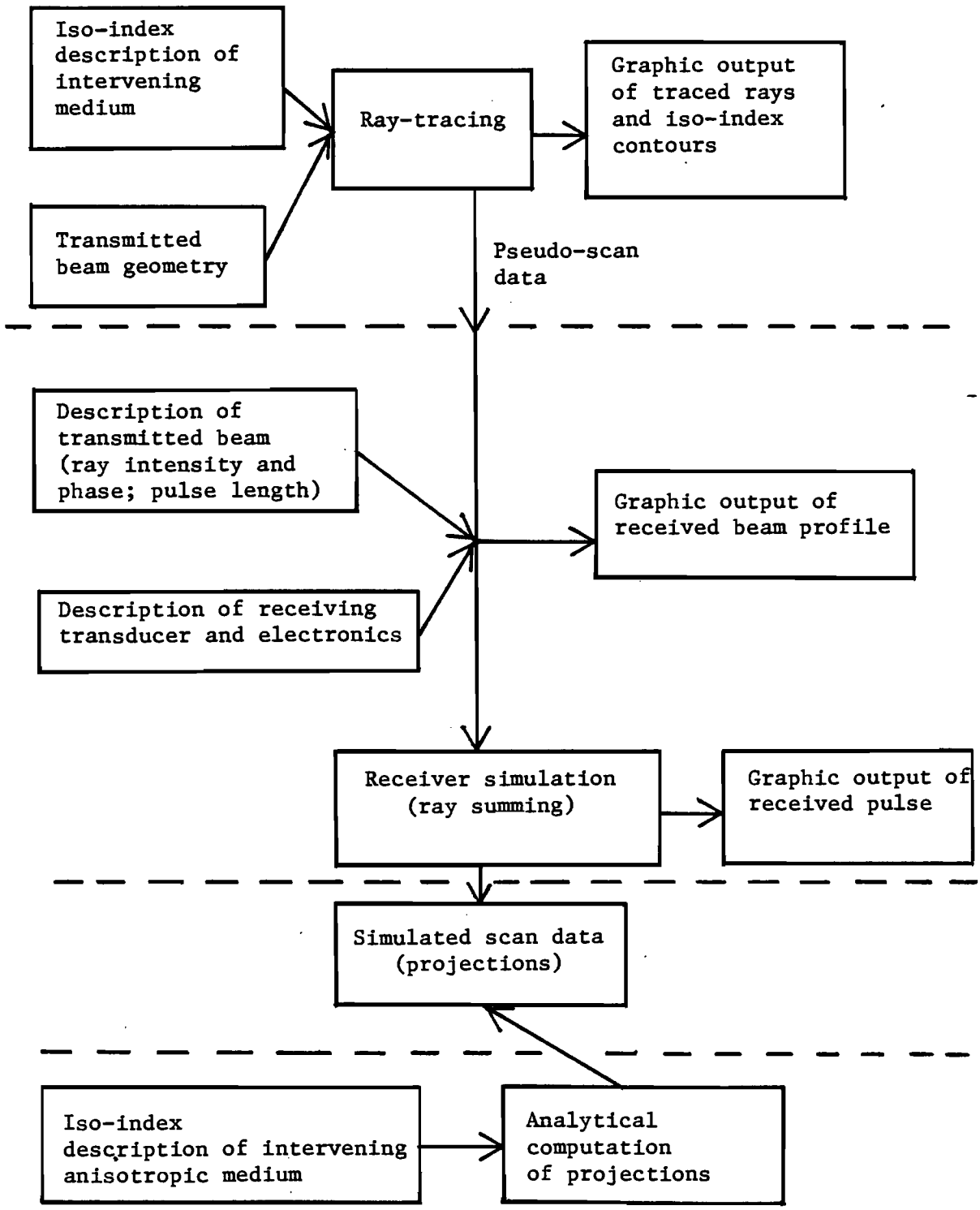



Figure 1.

Block Diagram of the Simulation Software

It is fortuitous that the integrator which is so effective as an AE detector is also simple to simulate. The sampled output of the integrator is equivalent to the sum of the intensities of the rays incident upon the receiver aperture, regardless of the shape of the transmitted pulse. Gating of the sinusoidal burst at the transmitter does not affect the integrated received intensity, but does determine the transmitted pulse bandwidth. While it is possible to include effects of finite bandwidth, a narrowband model was employed in this study.

To compute the peak of the envelope of the received PE signal, the entire time-course of the PE waveform must be evaluated. The time interval during which the receiving electronics are gated on is partitioned into intervals. Interval partitioning is defined both by the arrival times of rays and by the pulse durations of rays which have already reached the receiver. The peak amplitude within each interval is evaluated either by the phasor sum, if the interval exceeds one cycle, or by numerical evaluation for shorter intervals. The final step of the ray-summing phase is the generation of a simulated tomographic scan. Graphic output of individual simulated received piezoelectric signals also is available. A separate portion of the simulator also computes the ultrasonic beam profile at the plane of the receiver. Spatial moments of the beam also are computed and graphic output is provided.[3]

B. Comparison of Simulation with Experiment

We present two case studies comparing measured tomographic projections with simulations. For this study, only well-characterized tissue phantoms were employed.

Beam Profiles for Samples of Castor Oil and Saline

To demonstrate the accuracy of the ray-tracing method, beam profiles at the plane of the receiver are compared with experimentally determined profiles. A point-like 1.2 mm piezoelectric element was mechanically scanned over a portion of the receiver plane to measure the beam profiles.[3] The transmitter was a 5-MHz broadband, focused transducer with a 5-cm focal length. For the simulation we employed a focused-beam model, and fit the $(J_1(x)/x)^2$ profiles to empirical data.

The beam profile is effectively shifted relative to the central axis of the transmitted beam when the beam is moved through the edge of an object. A small apparent shift occurs when the object is attenuating and only part of the beam passes through the object. Alternatively, the beam can experience a physical displacement as a result of refractive bending. We demonstrate these two cases with two extremes: castor oil which is attenuating but not severely refracting, and saline which exhibits little loss but whose velocity is significantly higher than that of water alone.

Figure 2 illustrates the effect of moving the beam through a fingercot filled with castor oil. At 20°C the refractive index was 0.99 and the attenuation at 5 MHz was 1.4 $cm^{-1}$. In part a) are shown the beam profiles across

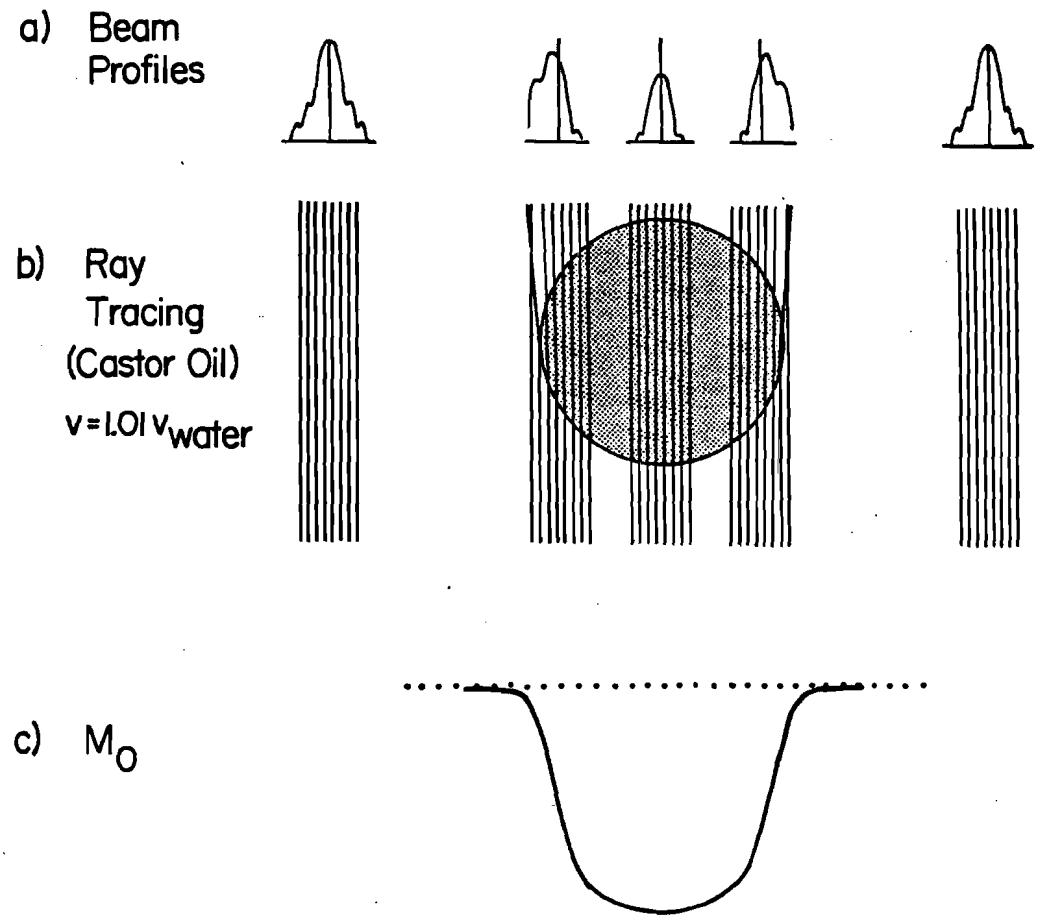



Figure 2.

Panel a) illustrates beam profiles obtained by simulation of a cylindrical castor oil sample shown in panel b). The zeroth moment, a measure of the intensity at the receiving aperture, is plotted to scale in panel c).

the 6 mm aperture corresponding to a water-only path, paths partially intersecting the edges, and a path through the center. Selected rays of each beam in part b) illustrate the small refractive bending. Part c) is the zeroth order moment of the beam $M_o$ (vertical axis) plotted against the position of the beam (horizontal). Each point on the $M_o$ curve is analogous to the time-integrated acoustoelectric response and is the sum of the intensities of each of the rays.[3] Thus, the $M_o$ plot is equivalent to the tomographic projection of attenuation measured with a large-aperture acoustoelectric receiver. Figure 3 illustrates the corresponding experimental determination. The simulation yields beam profiles and $M_o$ very similar to the experimental result, and corroborates the apparent beam shift due to the attenuation in castor oil.

We illustrate the effects of the significant refraction in saline in Figure 4. An 8% saline solution at 20°C yielded a refractive index of 0.94 and an attenuation less than 0.01 $cm^{-1}$ at 5 MHz. The beam profiles are severely distorted and shifted (part a) as would be expected from the bending of the rays evident in part b). We illustrate the beam displacement with the normalized first spatial moment of the beam[3] plotted in part c). This metric is analogous to the centroid and is defined by

$$M_1/M_o = \int_A I(\vec{r})\,r\,dA \Big/ \int_A I(r)\,dA$$

where $I(r)$ is the received intensity at the sample point in the receive plane located $\vec{r}$ from the central axis of the transmitted beam. The limits of integration correspond to an aperture of area A in the receiver plane. Thus, $M_1/M_o$ yields the mean displacement of the beam as a function of the position of the transmitter, as the beam is scanned through the saline. We illustrate in Figure 5 the corresponding experimental results. The $M_1/M_o$ plot from simulation shows excellent agreement with experiment. Simulated beam profiles show good agreement with experiment but are subject to sampling limitations of the 100-ray beam. The beam profiles both experimentally and in simulation are very sensitive to position when the incident beam intersects the edges of the sample. In contrast, $M_1/M_o$ appears to be a stable metric despite the variability in the individual profiles.

Projections of a Castor Oil Phantom

To further test the accuracy of the simulation, a comparison was made with piezoelectric measurements of attenuation in castor oil. Measurements were made using a CdS crystal first as a piezoelectric and then as an acoustoelectric receiver. A sample of castor oil contained in a thin, cylindrically shaped latex membrane was scanned using a 1.27 cm aperture planar transmitting transducer. Castor oil was selected because its low-megahertz attenuation is comparable to that of tissue and its acoustic velocity is only slightly greater than that of water at 20° C, n = 0.99. The resulting small refraction does not bend the beam significantly, but does give rise to significant phase cancellation in the piezoelectric receiver. The ray geometry of the near-field model for the planar transmitter was appropriate for the approximately 19-cm transmitter-receiver spacing with the object centered between the transducers. We used a Gaussian beam profile fit to empirical data. Over the

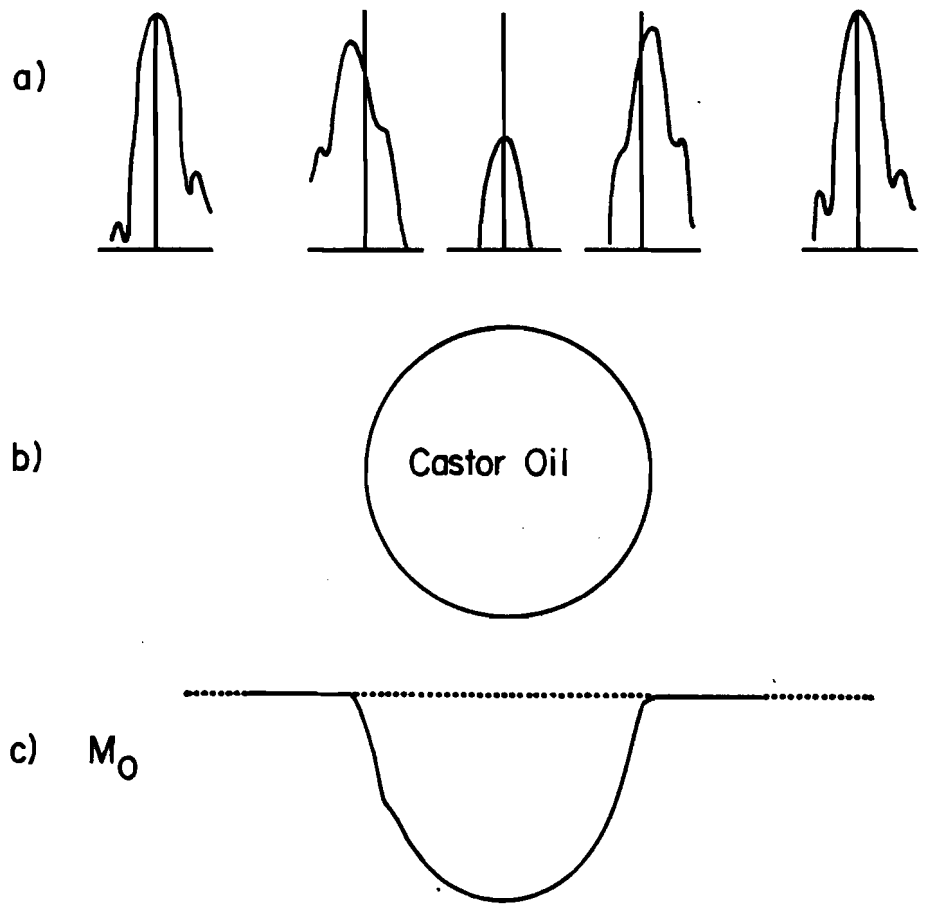



Figure 3.

Panel a) illustrates experimentally measured beam profiles for transmission through a castor oil sample shown to scale in panel b). The intensity at the receiving aperture, the zeroth moment, is shown in panel c).

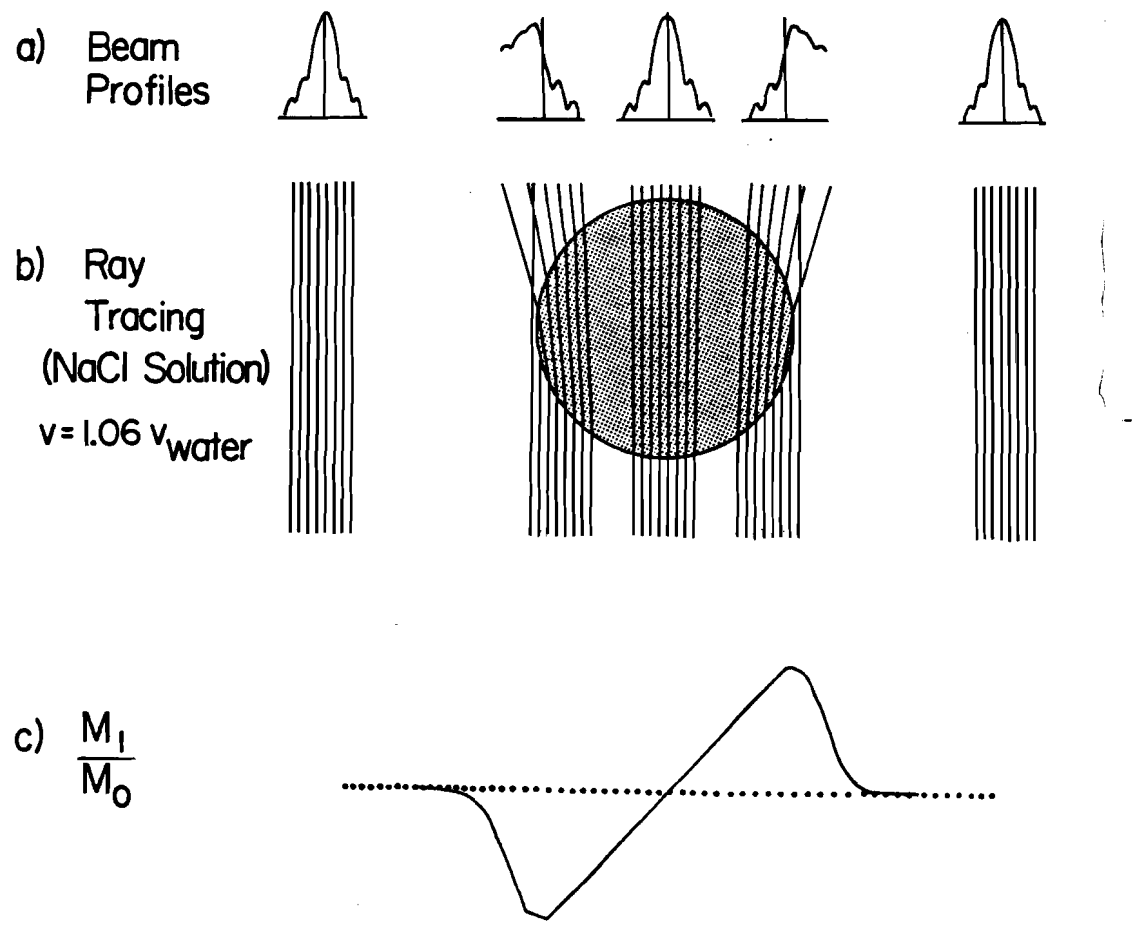



Figure 4.

Panel a) illustrates beam profiles obtained by simulation of a cylindrical saline sample shown in panel b). The ratio $M_1/M_0$, a measure of the lateral deviation of the beam, is plotted to scale in panel c).

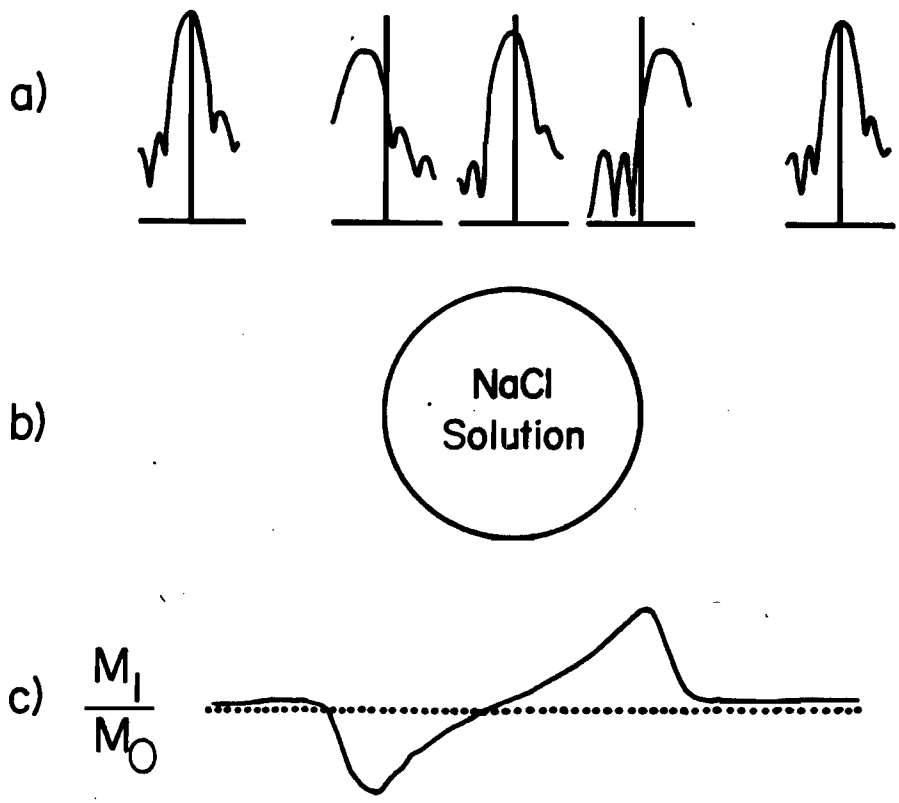



Figure 5.

Panel a) illustrates experimentally measured beam profiles for transmission through a saline sample shown to scale in panel b). The lateral deviation of the beam is shown by the ratio $M_1/M_o$ in panel c).

3-6.5 MHz range the beam width was approximately 2.5 cm at -40 db from the peak of the main lobe. We compare in Figure 6 the experimentally determined piezoelectric projections (solid line) and the simulated projections (dashed line) at 3.5 and 4 MHz in a) and b) respectively. Figure 7 compares the same projections as measured with an acoustoelectric receiver (solid line) and as simulated (dashed line). We observe from these results: a) the overestimation of attenuation in the piezoelectric projection is substantially larger than in the acoustoelectric, thus it is due primarily to phase cancellation rather than refractive beam bending; b) based upon the acoustoelectric projections, both the transmitted beam model and the assumption of negligible diffraction appear valid for this example; c) the small asymmetry in the measured acoustoelectric projection is due presumably to the receiver aperture which was trapezoidal rather than rectangular as assumed in the simulation. This conclusion is corroborated by the absence of asymmetry in the projection computed from $M_0$ (Figure 3); d) it appears that the piezoelectric simulation underestimates the phase cancellation error because of undersampling of the beam. The 100 rays of the beam were spaced 0.25 mm apart, corresponding to $0.58\lambda$ and $0.66\lambda$ spacings at 3.5 MHz and 4 MHz, respectively. Amplitude variations at the receiver over fractions of a wavelength are small, thus the acoustoelectric simulation is uncompromised. However, even over a fraction of a wavelength, the phase varies significantly. Therefore, more dense beam sampling may be required to simulate phase-dependent measurements.


1. G. H. Brandenburger, "Simulation of Ultrasound in Tomographic Imaging: Theory and Methods Based on Geometrical Acoustics," BCL Monograph No. 397, May 1981.

2. J. R. Klepper, G. H. Brandenburger, J. W. Mimbs, B. E. Sobel, and J. G. Miller, "Application of Phase Insensitive Detection and Frequency Dependent Measurements to Computed Ultrasonic Attenuation Tomography," IEEE Transactions on Biomedical Engineering, BME-28, no. 2, pp. 186-201, 1981.

3. T. A. Shoup, G. H. Brandenburger, and J. G. Miller, "Spatial Moments of the Ultrasonic Intensity Distribution for the Purpose of Quantitative Imaging in Inhomogeneous Media," Proceedings of the IEEE Ultrasonics Symposium Catalog No. 80CH1602-2, pp. 973-978, 1980.

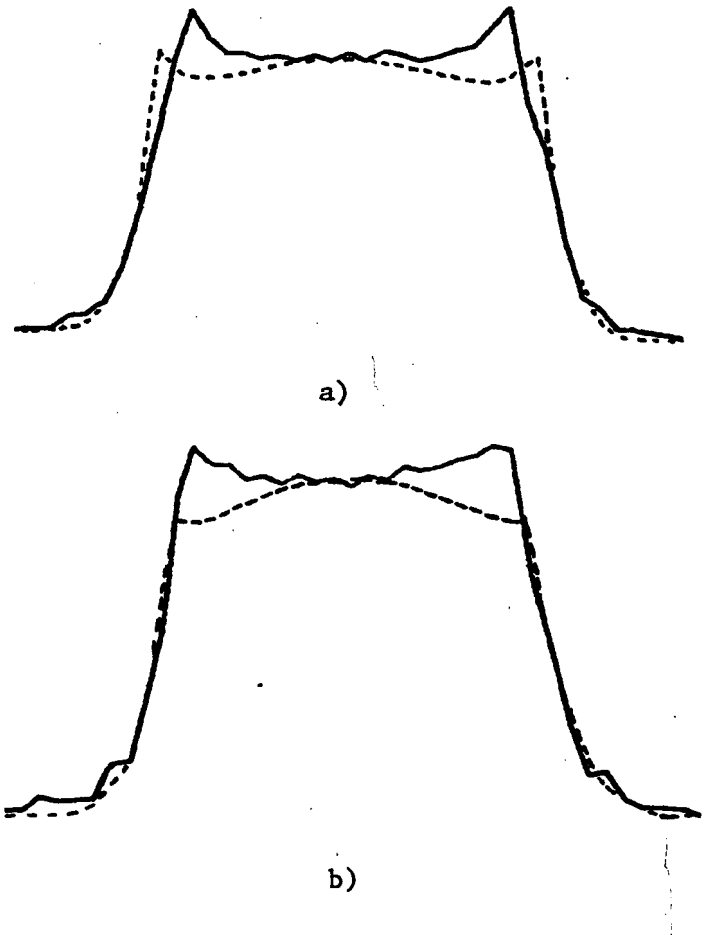
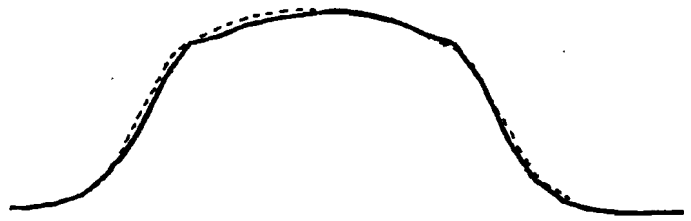
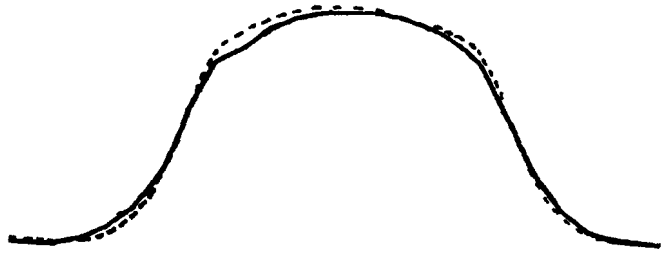



Figure 6.

Compared at 3.5 MHz (panel a) and 4 MHz (panel b) are projections of attenuation in a cylindrical sample of castor oil measured with a 1.27 cm aperture piezoelectric receiver (solid curves) and from simulation (dashed curves).



a)



b)

Figure 7.

Compared at 3.5 MHz (panel a) and 4 MHz (panel b) are projections of attenuation in a cylindrical sample of castor oil measured with a 1.27 cm aperture acoustoelectric receiver (solid curves) and from simulation (dashed curves).

B-3. Anisotropy in Ultrasonic Attenuation and Its Implications for Computed Transmission Tomography

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J. G. Miller, BCL
J. E. Pérez, M.D., Medicine

Support: RR 00396
HL 17646

Systematic geometric variations in the acoustic parameters of tissue, whether due to pathology or intrinsic to normal tissue, have potential use in ultrasonic tissue characterization. At other laboratories as well as ours, a variation in ultrasonic attenuation with angle of propagation relative to muscle fiber orientation has been noted in skeletal and cardiac muscle.

In addition to its potential usefulness as a tissue signature, anisotropy of attenuation and possibly of other parameters has serious potential for corrupting the results of any measurement system which combines measurements made at multiple angles of view. However, few data exist to document either the existence or magnitude of anisotropy in normal tissues. Furthermore, no studies have been reported which address the question of whether changes in anisotropy accompany specific pathologies.

As an approach to these questions, we are conducting studies on several tissue types, specifically normal and infarcted myocardium, normal skeletal muscle, and normal liver parenchyma. Preliminary results on a rectangular parallelepiped excised from normal dog left ventricle were presented last year (PR 16, B-4). We present here the preliminary results obtained from skeletal muscle and liver.

Cylinders (2 cm diameter) were cut from the intact excised organs and were mounted in a bath of isotonic sodium citrate solution for scanning. Muscle specimens were mounted with the fibers in the plane of the scan. Liver specimens were obtained at several orientations relative to the capsule of the liver. Samples were massaged gently in the bath to expel bubbles of air, and were allowed to come to temperature equilibrium with the fluid bath.

Scan lines were obtained at 3-degree intervals through 360 degrees. A filter which compensates for the frequency dependence of the transmitted beam was applied, and the slope of attenuation with frequency was computed over a range from 3.0 MHz to 6.5 MHz.

A measure of the anisotropy present is given by the zeroth-order moments of the scan lines at each angle. These normalized measures are plotted for skeletal muscle and liver in Figure 1. We note that liver is isotropic whereas skeletal muscle exhibits a variation in the slope of attenuation of approximately 4.5 to 1, with maximum slope occurring when the ultrasound propagates parallel to the muscle fibers. This orientation for maximum attenuation is consistent with that observed by Nassiri, Nicholas, and Hill.[1]

An apparent error in interpretation of previously published data has led to widespread confusion on this point as a result of statements in the review by Wells[2] that attenuation is maximum for ultrasound propagated perpendicular to muscle fibers.

1. D. K. Nassiri, D. Nicholas, and C. R. Hill, "Attenuation of Ultrasound in Skeletal Muscle," Ultrasonics, vol. 17, pp. 230-232, 1979.

2. P. N. T. Wells, "Physical Principles of Ultrasonic Diagnosis," Academic Press, London and New York, 1969.

## B-4. Adaptive Pulse-Echo Imaging for Ultrasonic Tissue Characterization

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K. V. Gurumurthy, M.S., Electrical Engineering

Support: RR 00396
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Conventional linear phased-array imaging systems permit steering and focusing an ultrasonic beam to form a qualitative two-dimensional image which typically covers an 80-degree sector. These systems assume that the insonified medium is homogeneous. Tissue is not. Previously we showed that homogeneous-medium beamformers produced large errors in estimates of the attenuation coefficient of tissue (PR 16, B-5). We have extended that study in three ways:

1) A dispersive tissue model was developed which can be synthesized from any experimental attenuation data,

2) A maximum-likelihood estimator for the attenuation coefficient in the presence of random scatters was derived, and

3) A 15-channel control circuit for steering and focusing the beam of a transducer array was designed and built.

The usual linear-phase tissue model is non-causal and leads to errors in the calculation of attenuation coefficient based on time-domain measurements. Previously we described a dispersive model based on the Hilbert transform, which gave accurate time-domain values and which we used in simulations of beamforming techniques (PR 16, B-5). The Hilbert model assumes that attenuation is linearly dependent on frequency. The all-pole model which we developed can be synthesized from data with an arbitrary dependence on frequency.[1] Its transfer function is

$$H(s) = e^{-j\omega\tau} \sum_{i=1}^{N} \frac{A_i}{s+P_i} \qquad (1)$$

where $P_i$ is the location of the ith pole and $\tau$ is the bulk delay associated with the transfer function. The coefficients $A_i$ are found by extracting the roots from a polynomial fit of the squared magnitude of the measured transfer function. The transfer function contains no zeros and has poles only in the left-half plane because it was assumed that the transfer function was stable, minimum-phase, and realizable. A single-pole model proved to be a good fit for most existing experimental data in the 1-10 MHz range. Its electrical equivalent is a low-pass RC filter with a scale factor and a bulk delay. This dispersive model was in good agreement with the Hilbert model, so that the use of the Hilbert model in the simulations was further justified.

The magnitude of the measured frequency response of tissue depends on the width of the ultrasound beam and upon the area of the transducer elements. This dependence follows a Rayleigh fading-channel model for random scatterers and a Rician fading-channel model for random scattering in the presence of specular reflectors.[1] The effects of non-zero beamwidth and transducer area appear as error terms in the attenuation estimate even with perfect beamforming. Approximation of the probability density function of these error terms with the density function of a Gaussian random variable permitted derivation of a maximum-likelihood estimator for the attenuation coefficient. The variance of this estimator decreases as bandwidth and the number of transducer elements is increased.

In order to implement measurements of attenuation on gelatin tissue models and tissue samples, we designed and built a 15-channel latch-counter and driver circuit to steer and focus our 32-element linear array transducers. Delay values for point or axicon focus are generated in a minicomputer (TI-980) which is directly interfaced to the transmitter circuitry. Delay values for each transducer element are latched. The transmit command initiates a count-down of the latched value. A clock frequency of 40 MHz gives a delay increment of 25 ns. This delay quantization corresponds to a distance of about 0.04 mm and is roughly one-tenth the delay correction required for adaptive beamforming in a simple two-layer tissue model (PR 16, B-5). Thus we should have adequate resolution for appropriate beamforming on transmit. Although this circuitry is operational, it has not yet been connected to a transducer. Once it has been connected we will use the single-channel, dual-microprocessor echo-cardiograph (PR 15, A-17) as a receiver in studies of static targets. Obviously, in this case beamforming must be done off line, but such a scheme will allow arbitrary temporal quantization for beamforming of the received signal.

1. K. V. Gurumurthy, "Adaptive Pulse-Echo Imaging for Quantitative Ultrasonic Tissue Characterization," Department of Electrical Engineering, Washington University, St. Louis, Missouri, August 1981 (D.Sc. Dissertation).

B-5. Resolution of Linear Phased Arrays for Ultrasonic Imaging

Personnel: R. M. Arthur, BCL
T. H. Morrison, B.S., Electrical Engineering

Support: RR 00396
Washington University

Simulations of the performance of single-element ultrasonic transducers for studies of resolution in M-mode echocardiograms (PR 16, A-17) were improved so that we could characterize the pulse-echo imaging capability of linear transducer arrays. The transducer model now permits studying the effects of array geometry, form of the pulse excitation, and mode of focus on the performance a linear transducer composed of rectangular elements.[1]

Pressure patterns generated by the array were found by convolving the impulse response of the array with an excitation function. Three commonly used functions were evaluated: a four-cycle tone burst, a three-cycle burst with a half-sine envelope, and a five-cycle burst with an exponentially decaying envelope. The typical array that was simulated contained 16 elements with a one-wavelength width and two-wavelength spacing at 2.25 MHz. The unfocused and focused impulse responses for this geometry are shown in Figure 1. Both point and axicon focus were tested. With axicon focus insonification and beamforming are performed over a focal zone rather than at just one pixel. The advantage of axicon focus is reduced processing time, but at the cost of some degradation in image quality.

Once pressure patterns had been generated they were reflected from point targets in the medium insonified by the transducer, which was assumed to be homogeneous. Reflected waves received at the transducer produced transducer element outputs which were combined with appropriate delays for both point and axicon focusing schemes. The peak of the beamformer output was detected and used to measure the resolution of the array. For a given set of targets the beam was swept from 45 degrees on one side of the transducer axis to 45 degrees on the other at a constant focal radius. Various combinations of transmit-and-receive focus modes for each of the excitation functions was studied to determine the maximum received signal in relation to near side lobes and grating-lobe contamination and to determine the effective width of the beam at specific locations in the image field of the array. Beamwidth ranged from 1.6 mm at a range of 5 cm on axis to 7.0 mm at a range of 15 cm, 45 degrees off axis. Focus mode had little effect on beamwidth except off axis in the near field. To confirm that resolution could be inferred from the beamwidth of a single point target, we scanned two point targets with various separations. Figure 2 shows the array response for one fixed point on axis and a second point which is moved perpendicularly to the axis. They must be separated by between 1.5 and 2.0 mm in order to be resolved. The beamwidth for this case (1.6 mm) is in this range. Other tests confirmed the relation between beamwidth and resolution.

The primary limitation of this performance model is the assumption of a homogeneous medium. We plan to combine the tissue model described in

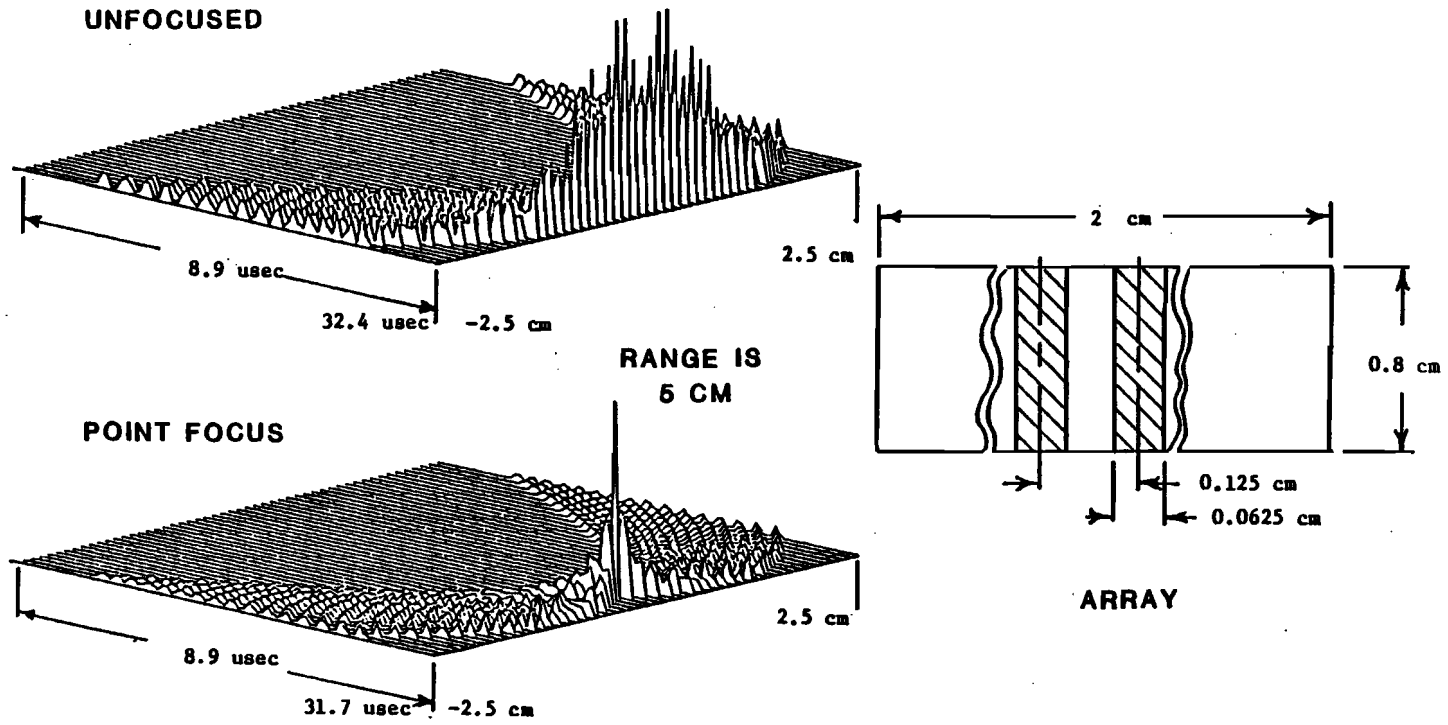


Figure 1.

**Impulse Response of a 16-Element Array**

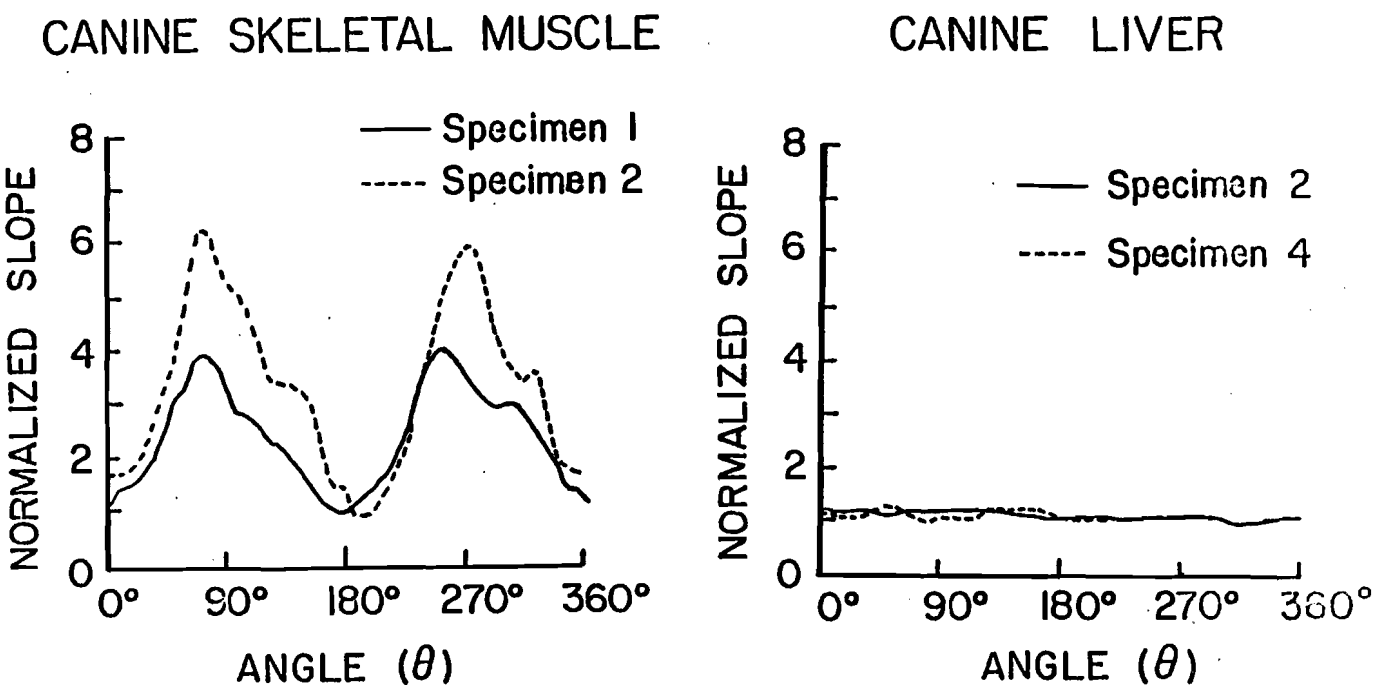


Figure 1.

Normalized slope of attenuation is plotted as a function of angle of propagation for two types of tissue. The data in the left panel were obtained from canine skeletal muscle. Note that the angle 90° corresponds to propagation parallel to the muscle fibers. The data in the right panel were obtained from canine liver, with arbitrary orientation.

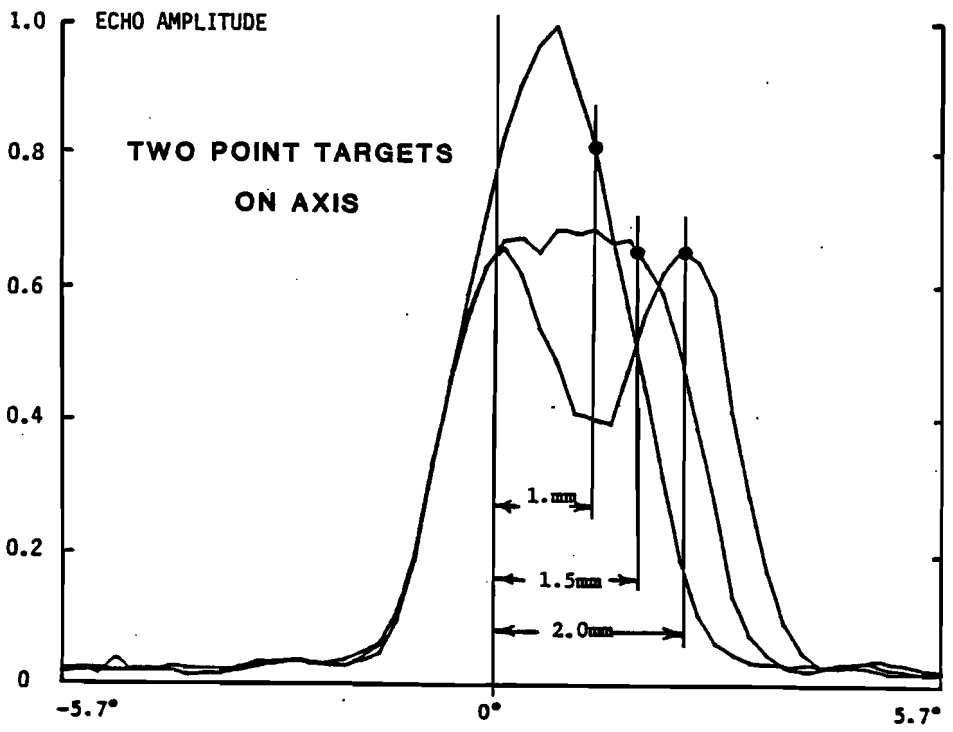


Figure 2.

## Resolution with Point Focus

section B-5 with the array model to determine the actual resolution that can be achieved in tissue.

1. T. H. Morrison, "An Ultrasonic Phased-Array Performance Model for Medical Imaging," Master of Science thesis, Department of Electrical Engineering, Washington University, St. Louis, Missouri, August 1981.

## B-6. Algorithm Development for Radiation-Treatment Planning

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Support: RR 00396
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We have continued our previously described (PR 16, B-14) software-development efforts for implementing the "delta-volume" method[1,2] (PR 13, I-3; PR 14, G-6; PR 15, G-4) of computing three-dimensional absorbed-dose distributions for radiation-treatment planning using macromodular hardware[3] (B-7; PR 16, B-15). We have completed preliminary tests of our algorithms (B-7) using electron-density matrices derived from computed-tomography scans of the RANDO phantom (PR 14, G-6) in which experimental dosimetric measurements also have been made.[4] Our intent is to compare these measurements with the computed results for the same irradiation-field geometry in the phantom. Similarly, we plan to compare computed results corresponding to the existing data for rectangular fields in water.[5] These goals can be achieved when we complete the prior task of transforming the scatter-air-ratio water data from the right circular-cylindrical coordinate system in which they are presented[5] to the Cartesian system so that we can use them in our algorithms.

1. J. R. Cunningham, "Scatter-Air Ratios," Physics in Medicine and Biology, vol. 17, pp. 42-51, 1972.

2. K. B. Larson and S. C. Prasad, "Absorbed-Dose Computations for Inhomogeneous Media in Radiation-Treatment Planning Using Differential Scatter-Air Ratios," Proceedings of the Second Annual Symposium on Computer Applications in Medical Care, IEEE Computer Society, Long Beach, California, pp. 93-99, 1978.

3. C. E. Molnar, F. U. Rosenberger, and R. A. Arnzen, "Macromodular Computer Design. Part 3: Restructured Macromodules," Final Report, Contract SD-302 (ARPA), Computer Systems Laboratory, Washington University, St. Louis, Missouri, February 1974.

4. S. C. Prasad, G. P. Glasgow, and J. A. Purdy, "Dosimetric Evaluation of a Computed Tomography Treatment System," Radiology, vol. 130, pp. 777-781, 1979.

5. H. E. Johns and J. R. Cunningham, The Physics of Radiology, Third Edition, C. C. Thomas, Springfield, Illinois, 1971.

## B-7. Macromodular-System and Array-Processor Implementations for Absorbed-Dose Calculations in Radiation-Treatment Planning

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Support: RR 00396

Substantial progress has been made in the hardware implementation of the Cunningham method (B-6; PR 13, I-3; PR 14, G-6; PR 15, G-4; PR 16, B-14) used for the computation of absorbed dose in radiation-treatment planning. A variety of hardware was employed in this implementation which included Phase I and restructured macromodules[1] (PR 16, B-15), a Texas Instruments TI-980 computer running under the MIST operating system, and an MMS-X display (B-8). In addition, several pieces of specialized hardware were fabricated to allow data communications between Phase I and restructured macromodules and to perform high-speed shifting and concatenation operations. The flexibility of the macromodules has permitted the configuration of a pipelined and concurrent structure that is computationally very efficient, and further, that is capable of providing output appropriate for displays of the results (B-8).

The irradiated-field volume for which the dose calculations are made is partitioned into a 16-by-16-by-16 array of 1-$cm^3$ voxels. Consequently, there are approximately $8 \times 10^6$ voxel-pair computations to be made in each problem solution. Broadly speaking, the task of carrying out these voxel-pair computations is divided between the Phase I and the restructured macromodules. Accordingly, the Phase I modules handle the address generation for table lookups and voxel-pair coordinate calculations, for which 12-bit arithmetic is adequate, while the restructured macromodules carry out the arithmetic computations, such as ray-attenuation integration, for which 16 bits of precision are needed.

At the beginning of each voxel-pair computation, the absorbing-voxel coordinates are incremented, and when necessary, the scattering-voxel coordinates are updated. The three algebraic differences between respective coordinates are then computed and the absolute values formed and concatenated to produce an address for the table lookup of the Klein-Nishina electron cross-section for the scattered ray, the logarithm of the differential scatter-air-ratio (SAR) data, and the integration step-size along the ray. Concurrently, the scattering-voxel coordinates are left-shifted by five positions and the algebraic differences of the coordinates are added. This has the effect of starting the integration at the midpoint of the first increment of path-length. The algebraic difference is then left-shifted one place for each subsequent step of the integration process. The most significant 4 bits of this 9-bit accumulating sum, when concatenated, produce a unique address that specifies the voxel in which the integration interval is found. This address is also used to look up the corresponding electron density of that voxel. In the restructured-macromodule system, two concurrent processes are now being carried out; these are the electron-density integration along the scattered ray and the multiplication of the step size by the Klein-Nishina cross-section in the matrix multiplier. At the completion of the integration, the finite summation is passed to the matrix multiplier where a final multiplication is made. The resulting product is then added to the logarithm of the appropriate element of the differential SAR matrix, and the result is passed to the TI-980 computer for incrementing the accumulating dose in the absorbing voxel. This result is maintained on the cable to the TI-980 computer until it is accepted. In the meantime, the macromodules begin a new voxel-pair computation.

The inventory of macromodular hardware required to carry out these steps include two Phase I pedestals, eight frame blocks, and seventy-five Phase I macromodules, while the restructured hardware set includes two base pedestals, six crates, and twenty-five restructured macromodules.

Running time of the macromodular portion of the algorithm for a $(16\text{-cm})^3$ field was measured to be 6 minutes and 40 seconds - well within the 9 minutes initially estimated before the system was built. When running in conjunction with the TI-980 computer, this time increases to 8 minutes, still maintaining a comfortable margin over the 9-minute estimate. Although there exists potential for further pipelining in the macromodular system, these measurements point out the fact that the TI-980 computer is currently the bottleneck; thus, efforts should be concentrated on that portion of the system to improve overall performance. To date, little experience has been gained from the hardware implementation because the main effort has been concentrated on further refinement of computational methods for transformation of the differential SAR data from the cylindrical- to the rectangular-coordinate system required for implementation of our algorithm (B-6). It is expected that continued activity during the coming year will provide valuable experience that can eventually culminate in a useful clinical tool.

1. C. E. Molnar, F. U. Rosenberger, and R. A. Arnzen, "Macromodular Computer Design. Part 3: Restructured Macromodules," Final Report, Contract SD-302 (ARPA), Computer Systems Laboratory, Washington University, St. Louis, Missouri, February 1974.

## B-8. Three-Dimensional Display of Absorbed-Dose Computation for Radiation-Treatment Planning

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Support: RR 00396

Our previously described efforts (PR 16, B-17) have continued in the development of methods for displaying the results of our method of computing three-dimensional absorbed-dose distributions for radiation-treatment planning (B-6, B-7; PR 13, I-3; PR 14, G-6; PR 15, G-4; PR 16, B-14, B-15). Several techniques currently are being evaluated for implementation in macromodular hardware.[1] These all involve the use of the MMS-X graphic-display system and include two- and three-dimensional contouring, plane-by-plane presentation with the dependent variable represented as altitude above the plane, two-dimensional intensity modulation, and three-dimensional intensity modulation of a defocused beam. Furthermore, the superposition of anatomical features as derived from computed-tomography scan data can be included in each of these techniques, thus providing essential points of reference for the treatment planner.

Our major goal is to develop one or more of these methods for the comprehensive and quantitative presentation of the three-dimensional dose distribution. Three-dimensional contouring and plane-by-plane intensity-modulation and altitude-presentation displays currently are operating, the software having been written over the past several months. Initial experiments with these techniques have been conducted employing absorbed-dose distributions computed on the basis of electron-density data derived from computerized-tomography scans of the RANDO phantom (PR 14, G-6). Each of these projection techniques has its own set of advantages and disadvantages. For example, three-dimensional contouring allows a quantitative assessment of a particular dose level, but it is difficult, using this method, to form a composite image of the dose distribution. On the other hand, intensity modulation can give an overall qualitative picture of the "hot" spots and "cold" spots in the distribution. In none of these experiments has the inclusion of anatomical features been attempted to date.

Currently, an MMS-X display CRT unit is undergoing electronic modification to permit dynamic defocusing of its beam by means of programmed input/output from the TI-980 computer. Three-dimensional intensity modulation of the defocused beam with superposition of anatomical features drawn with a focused beam will then be studied. Display software for this display technique must be able to update the coordinate position of the functional values in response to manual control input from joysticks and potentiometers and then replace the z coordinates of the updated vectors by functional values of the absorbed dose at the respective points. Since this is a relatively time-consuming process, it would produce a considerable amount of flicker on the CRT display if updating were done while the object were moving. A way to circumvent this problem would be to display anatomical

features only as the display is rotated. When the manipulation of these features has ceased, the dose-distribution vectors can be updated and the composite image drawn. This software development should begin in the near future.

1. C. E. Molnar, F. U. Rosenberger, and R. A. Arnzen, "Macromodular Computer Design. Part 3: Restructured Macromodules," Final Report, Contract SD-302 (ARPA), Computer Systems Laboratory, Washington University, St. Louis, Missouri, February 1974.

## B-9. Interactive Studies of Regions of Interest in PETT IV Images

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Support: RR 00396
HL 13851
HL 17646

Currently there is no mechanism which will allow the examination of arbitrary regions of interest in images obtained using the PETT IV system. The software being developed for the Interdata 7/16 (PR 12, B-4; PR-14, B-4) will allow a user to place an arbitrary region of interest onto an image interactively. The software provides abort and erase (full and partial region deletion), as well as automatic region completion. All of these functions are controlled via buttons located on a joystick. The buttons are periodically polled by the software.

The following modules have been written, tested, and debugged:

1. GETJOY

   This module is an assembly language device driver for the joystick. When invoked it returns the status (either on or off) of all the buttons on the joystick as well as the X position and Y position.

2. DISPLY

   This module brings the specified image into core, scales it appropriately, and displays the image on the monitor via a Ramtek graphic display system. This module calls two previously written routines, GRYDIS and DSKIO, to display an image and perform disk I/O, respectively.

3. CREGN

   This module allows the user to define that portion of the display which is of interest. That is, the user defines a rectangle of arbitrary size, using the joystick, which will contain the desired region. After this rectangle is defined, the full range of the joystick is confined to this area. This module calls GDDAT and GETJOY to extract joystick data.

4. TRACK

   This module allows the user to define an arbitrary region within the previously set limits. It calls PLOTL and ADDLST to update the display and record region points respectively. It calls ERASE to let the user interactively erase a part of the region that has been created. The abort feature is imbedded within the module TRACK. The modules mentioned also access GDDAT and GETJOY to extract joystick information.

5. GDDAT

   This module is always called before GETJOY. It is responsible for properly scaling actual joystick data so that it will fall into the limits specified by the user in CREGN.

Once a contiguous region has been formed using this software, the list of region points is sent to a routine called AREA, which is still under development. AREA is responsible for determining which pixels fall within the specified region. It then collects information from the original image data and produces certain statistics concerning the user-defined region. These statistics will include total number of pixels, average activity per pixel, total activity within the region, volume enclosed by the region, etc.

Plans to enhance this prototype system include multiple-region definition, semi-automatic homogeneity analysis, and multiple-image specification at run time.

B-10. PETT IV Cardiac Studies

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Support: RR 00396
HL 13851
HL 17646

This project was designed to determine whether positron-emission tomography (PET) permits in vivo quantification of regional myocardial metabolism in normal subjects, patients with ischemic heart disease, and patients with cardiomyopathy. Previously we have demonstrated that $^{11}$C-palmitate accumulates in regions of normal myocardium but not in regions of infarcted myocardium (PR 16, B-6). We also have demonstrated both in vitro and in vivo, in experimental animals, that the rate of disappearance of $^{11}$C-palmitate from myocardium is dependent upon the metabolic demands placed upon that tissue. In experimental animals, the extent of the regional depression of accumulation of $^{11}$C-palmitate detectable by PET correlated closely with the extent of myocardial infarction quantified enzymatically or morphometrically at necropsy in adjacent slices. Previous studies in man performed with PETT IV after the injection of $^{11}$C-palmitate intravenously have demonstrated a close correlation between the electrocardiographic site of infarction and the locus of metabolic derangement. There was a similarly close association between regions of abnormal left ventricular wall motion detectable by radionuclide ventriculography and regions of depressed palmitate accumulations demonstrable by PET. Further studies have demonstrated a close linear correlation between enzymatic estimates of infarct size and tomographic estimates of infarct size performed following intravenous injection of $^{11}$C-palmitate in patients with anterior transmural myocardial infarction.

During the past twelve months, research activities have focused on four problems: (1) the assessment with PET of regional myocardial metabolism of patients with congestive cardiomyopathy; (2) the development of techniques for the detection of right ventricular infarction and for the quantification of inferior myocardial infarction; (3) the determination of the natural history of the extent and distribution of myocardial injury during the first fourteen days after myocardial infarction; and (4) the assessment of the efficacy of orally administered nifedipine, a calcium antagonist, employed in the attempt to salvage jeopardized myocardium in the setting of acute myocardial infarction (tomographic estimates of infarct size are the primary end point).

Seven patients with cardiomyopathy and nine normal subjects were studied with positron-emission tomography after intravenous administration of 12 to 20 mCi of $^{11}$C-palmitate were uniform. In contrast, patients with

congestive cardiomyopathy exhibited both heterogeneity and marked regional depression of the accumulation of palmitate with as little as 25% of maximal regional accumulation even within regions of normal wall thickness estimated echocardiographically. In subjects with cardiomyopathy 34 $\pm$ 1.4% (SEM) of the myocardial volume exhibited decreased accumulation of palmitate in the range of 40 to 50% as maximal regional $^{11}$C-palmitate accumulation. Surprisingly, there was no striking difference between the clearance rates in regions with initially normal and abnormal palmitate accumulation in patients with cardiomyopathy (39.4 $\pm$ 2.1 vs 41.1 $\pm$ 5.4% per 10 minutes) nor was there any significant difference in clearance compared to clearance in control subjects (44 $\pm$ 3.0). Studies are currently underway to develop algorithms to provide quantitative estimates of the spatial heterogeneity of the distribution of palmitate in myocardium.

During the past year algorithms were developed to permit the quantification of myocardial infarction among patients with inferior infarction. Algorithms employed data acquired in a transaxial fashion but also utilized transaxial, sagittal, and coronal reconstructions to delineate the zones of normal and abnormal myocardium. A significant correlation was found between the extent of left ventricular infarction demonstrable by PET and global left ventricular ejection fraction determined by radioventriculography among patients with anterior and inferior myocardial infarction. The data fell along the same regression line indicating the validity of the estimates of left ventricular infarction observed in patients with inferior myocardial infarction. A linear correlation was also found between enzymatic estimates of infarct size and PET estimates of left ventricular infarction among patients with anterior myocardial infarction. In contrast, for patients with inferior myocardial infarction, enzymatic estimates of infarct size generally fell above this regression line determined for patients with anterior infarction indicating concurrent right ventricular injury.

Studies were initiated to assess the natural history of the size, location, and characteristics of the regions of metabolic abnormality detectable by PET in patients with acute myocardial infarction during the interval from the first hours to several weeks after the onset of infarction. Preliminary data indicate that there appears to be a slight decrease in the size of the region of metabolic abnormality detected by PET during the interval between the first 48 hours and five to ten days after infarction. Early recurrent infarctions have been documented by PET in several patients and have been manifested by an increased region of depressed accumulation of palmitate which occurred in contiguity with the initial infarction. We have been able to study patients as early as four hours after the onset of symptoms of infarction as part of these studies and as an integral part of the studies of the efficacy of nifedipine as a pharmacologic therapy to limit the extent of myocardial necrosis in acute myocardial infarction. The results of the study of nifedipine are blinded, but this study has demonstrated both the feasibility and the utility of PET as an end point for clinical studies.

B-11. In-Vivo Measurements of Regional Blood Flow and Metabolism in Brain

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HL 13851
NS 06833
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We have continued our previously reported efforts in the study of central-nervous-system hemodynamics and metabolism. Our immediate objective has been the development of techniques employing biochemically significant compounds labeled with cyclotron-produced isotopes (PR 15, F-3), suitable external-radiation-detection systems (PR 16, B-9; B-12), and appropriate mathematical models (PR 16, F-3) for the in vivo and regional study of basic biological processes and pathology within brain. Our ultimate goal is to use these techniques to provide the quantitative physiological and biochemical measurements in humans necessary to understand central nervous-system disease, as well as to formulate specific therapies and monitor their results.

Our previously reported studies of ammonia transport and metabolism in brain (PR 16, B-11) have been published.[1] During the past year, we have developed and validated methods for measuring, regionally and in vivo, cerebral-blood flow (rCBF) using positron-emission tomography. Our development of this tomographic technique (B-12) has allowed us to scan multiple sections of the brain simultaneously and rapidly (<1 min), and now permits us to make the quantitative measurements of local cerebral-blood flow in a manner directly analogous to the well-known tissue autoradiographic technique. Our method is based on a simple compartmental model, originally developed by Kety, that describes the transport of a flow-limited tracer in blood and in tissue. We assume that this model remains valid at the regional level, and have applied it for regional in-vivo studies in monkeys and in man using as diffusible tracers $H_2{}^{15}O$ and $^{11}$C-butanol. Oxygen-15-labeled water was chosen because of the ease of preparation and short physical half-life ($\sim$2 min) which reduces radiation dose and permits repeated examinations in the same subject. Carbon-11-labeled butanol was chosen for comparison with radiolabeled water because it does not exhibit diffusion-limited transport behavior even for cerebral blood flow as high as 180 ml $min^{-1}$ $hg^{-1}$, in contrast with the case for water. In the range of flows observed in these experiments (25 to 55 ml $min^{-1}$ $hg^{-1}$), the correlation between results obtained with the two tracers was excellent ($r = 0.924$). For situations in which rCBF can be anticipated to be higher, $^{11}$C-butanol is more suitable. The response

of the cerebral circulation to acute changes in arterial carbon dioxide tension was measured by this technique using $H_2{}^{15}O$ as the tracer. We are presently using our technique in the evaluation of a variety of patients with central nervous-system disease.

1. M. E. Raichle and K. B. Larson, "The Significance of the $NH_3$ - $NH_4^+$ Equilibrium on the Passage of $^{13}N$-Ammonia from Blood to Brain: A New Regional Residue-Detection Model," Circulation Research, vol. 48, pp. 913-937, 1981.

## B-12. PETT VI Development

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Support: RR 00396
HL 13851
NS 06833

The project goal of implementation and utilization of a positron-emission tomograph, PETT VI, has been achieved with all previously described (PR 16, B-9) design specifications realized. The reliability and maintainability of the device are such that only minor adjustments are required every few days, and the time between repairs due to failures approaches several weeks.

The successful implementation of a PE-3242 host processor and RM-9400 video display has made an expeditious contribution to the project in allowing a multitask, multiuser environment to support concurrent activities of data collection, processing, image analysis and program development. Modularized software concepts have been implemented which emphasize flexibility in such matters as reconstruction filter, corrections for attenuation and random coincidences, and region-of-interest analysis.

Of particular interest is a recently developed data-collection protocol called dynamic frame acquisition. A user specifies the desired time frame and the total number of consecutive frames to define a continuous collection period. Postcollection sorting allows each frame to be processed independently of others, or summed with adjacent frames prior to processing. This protocol is ideally suited for the study of temporally dependent metabolic processes.

Future developments of the PETT VI system will be aimed at enhancing its utilization. Areas to be investigated include implementation of a graphics tablet for region-of-interest analysis, three-dimensional surface display generation, simultaneous display of transmission CT images with PET images, improvement of reconstruction speed with possible use of an array processor, and application of artificial-intelligence techniques in image analysis.

## B-13. PETT IV Experimental Studies

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Support: RR 00396
HL 13851
HL 17646

The aim of this project is to evaluate procedures required to translate results obtained with selected positron-emitting tracers used to characterize metabolism and perfusion in isolated hearts and in intact, open-chest dogs in which tracer kinetics are quantified with an isolated-probe system, to intact animals in which tracer kinetics are recorded by fast-scan positron-emission tomography. Such studies are intimately related to clinical activities undertaken with PETT IV in which static imaging is possible. However, data obtained with the isolated-probe data-acquisition system have demonstrated that a great deal of information can be obtained with sequential scanning used to characterize the uptake, accumulation, and clearance of myocardial tracers whose kinetics have been characterized in isolated perfused hearts and open-chest intact dogs.

Previous studies have shown that regional clearance of $^{11}$C-palmitate assessed by sequential tomography was consistently exponential from 5 to 15 minutes after intravenous administration of tracer. However, with coronary stenosis sufficient to induce ischemia without infarction, regional $^{11}$C-clearance became markedly heterogenous and the slope of the washout curve was significantly decreased. Thus, sequential positron tomography after intravenous injection of $^{11}$C-palmitate delineated zones of viable but ischemic myocardium that characteristically exhibited impaired oxidation. During the past year, we have been studying the effects of reperfusion after selected

intervals of coronary occlusion. Documentation of restored metabolism in ischemic myocardium was studied in 13 closed-chest dogs with positron emission tomography utilizing PETT VI. Cardiac PETT scans with 15 mCi of $^{11}$C-palmitate introduced intravenously were performed at selected intervals after thrombosis. Jeopardized regions were defined based on accumulation of less than 50% of maximal regional activity. After thrombolytic therapy, resulting in angiographically demonstrable reperfusion, repeat PETT scans after a second injection of tracer were performed and demonstrated that metabolic salvage of ischemic myocardium can be delineated objectively in vivo by PETT and that salvage induced by thrombolysis is dependent upon the time of its initiation after infarction. Analogous clinical studies should help define the temporal constraints of thrombolytic therapy in patients with acute myocardial infarction.

In additional studies completed within the past year, we have extended results obtained initially in isolated perfused hearts using a potentially useful perfusion tracer, $^{11}$C-butanol. In these studies, dogs with ischemia induced by occlusion of the left anterior descending coronary artery were given an exponentially increasing infusion of $^{11}$C-butanol, a tracer with a tissue/blood partition coefficient of 1.0. Programmed exponential infusion was utilized to achieve a steady-state value of a function derived from the monotonically increasing tissue concentration of tracer measured over time, enabling quantification of myocardial perfusion validated with 68-Ga microspheres as well as by invasive tissue biopsy and well-counting at the completion of the experiment. The results indicate that accurate quantification of myocardial perfusion is possible by fast scanning positron-emission tomography. However, the present sensitivity and resolution of instrumentation is not yet adequate. Thus, although regional differences and linear correlations with microspheres were demonstrable, absolute values of myocardial flow could not be determined tomographically because of limited spatial resolution. These limitations should be overcome with availability of the more sensitive positron-emission system currently under construction (SUPER PETT). Experiments performed in open-chest animals and employing tissue analysis have demonstrated that the exponential infusion of a diffusable radiotracer, such as $^{11}$C-butanol, does provide accurate quantification of myocardial perfusion verified by direct measurements with radioactive microspheres.

Studies planned for the next year will evaluate the efficacy of reperfusion therapy at selected intervals after acute occlusion of the left anterior descending coronary artery. In addition, a newly developed dynamic program, enabling rapid sequential data acquisition, will be utilized after injections of $^{11}$C-palmitate in intact dogs subjected to selected pharmacological and hemodynamic interventions in order to evaluate and characterize the tracer kinetics in intact animals and to compare them to those identified and characterized previously in isolated perfused hearts and open-chest dogs.

B-14. PETT Time-of-Flight Data Acquisition System Development

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Support: RR 00396
HL 25944
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Positron-emission transaxial tomographic scanners produce cross-sectional images of the body showing the spatial distribution of positron-emitting radionuclides which are concentrated by biochemical or physical processes in regions of interest. Utilization of PETT for dynamic imaging within the thorax and the head has necessitated technological developments which improve instrument sensitivity as well as decrease radiation dosages to patients and provide shorter scanning durations.

The current development of a new instrument, SUPER PETT, utilizing scintillators of cesium flouride (CsF) and a high-speed acquisition and preprocessing system will utilize information about the differential time-of-flight (TOF) of annihilation photons and is expected to achieve a sensitivity improvement of a factor of ten or better over the current thoracic scanner PETT IV. Experiments and theoretical studies of reconstructions utilizing time-of-flight data have been conducted (B-15, B-16, B-17, B-18, B-19).

A number of data-collection and processing strategies are summarized in Figure 1. Each detected photon-coincidence event produces an event-tuple $(\theta_{ij},d,t_{TOF})$ which augments the familiar tomographic projection data with a measure of the differential TOF. Given the need to quantize TOF measurements in the range of 5 to 10 bits (B-19), the quantity of digital data is increased by one to three orders of magnitude producing serious storage implications for the conventional list and no-loss-array collection modes.

A novel preprocessing architecture for the data acquisition system accomplishes on-line TOF calibration for long-term detector-pair variations, sensitivity normalization, attenuation correction and cell-position calculation for both the projection array and the most-likely-position array collection modes. Partitioning the acquisition system on a processor-per-view-plane basis (4 detector rings, 7 view planes for SUPER PETT) reduces the anticipated event rates to less than 200,000 events per second per processor. The acquisition system is shown in block-diagram form in Figure 2. Each detector has an associated electronics channel consisting of a high-gain, fast-timing photomultiplier tube and constant-fraction discriminator.

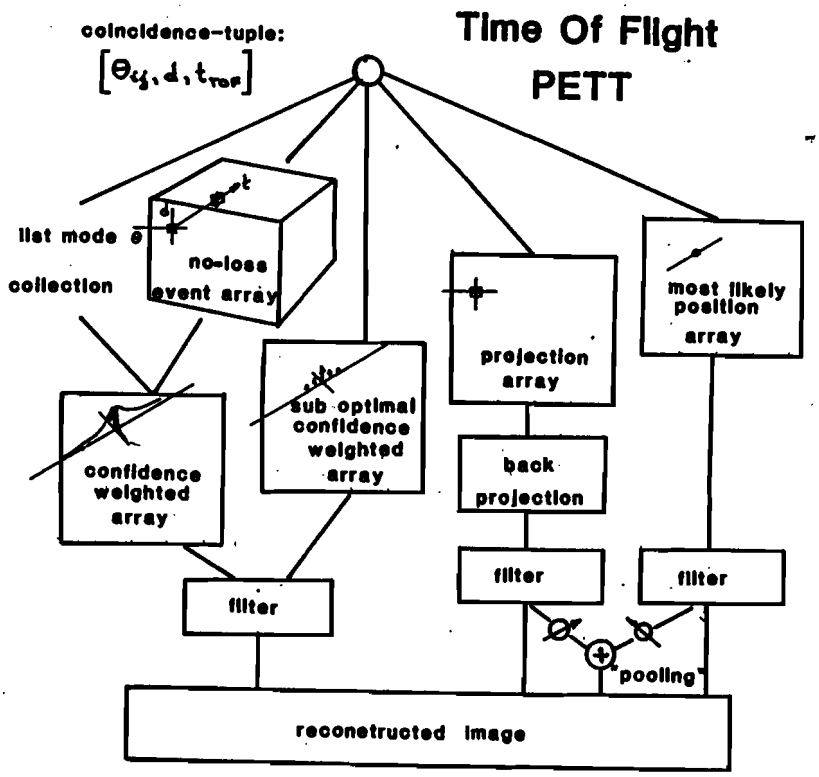


Figure 1.

Data Acquisition and Processing Modalities

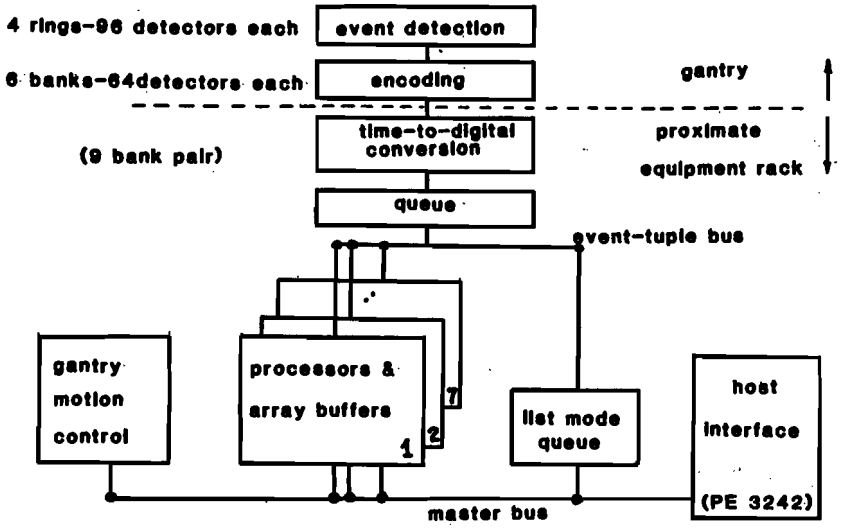


Figure 2.

Acquisition System Architecture

After encoding all channels into six detector banks, circuits resolve all detected coincidence events into nine bank-pair groupings. Each bank-pair grouping has an associated time-to-digital encoder. The time-to-digital encoding is achieved by time-to-amplitude conversion (TAC) followed by analog-to-digital conversion (ADC). The TAC is a capacitive charging circuit triggered by a start/stop pulse combination from the detector banks. A timing window of 6 ns is used to reject random coincidences while accounting for timing uncertainties and variations. The ADC has a pulse-height conversion time of 50 ns.

Each encoded coincidence vector is routed to an appropriate derandomizing FIFO. These have a maximum input rate of 10 MHz which is the determining factor of counting "dead-time." The outputs of these FIFOs are sequentially polled and routed to another set of seven view-plane FIFOs. Each view-plane FIFO provides data to a specialized processor. An additional data path permits direct transmission to the host processor for list-mode collection.

Each specialized processor is a microprogrammable machine realized by AMD 2900 family bipolar bit-slice components. They utilize the vector information to update two pre-image array buffers; a conventional "projection" array and a "most-likely-position" array derived from time-of-flight information. Both are realized in semiconductor memory. Normalization and calibration with regard to detector efficiency, attenuation, wobble position and long-term drift in time-of-flight detection are performed while a polar-to-rectangular coordinate transformation is carried out on the vector. Event-processing time is under ten microseconds with a microprogrammable cycle time of 160 ns minimum. Speed is enhanced by a pipelined architecture and a 12-bit hardware multiplier. Dual array buffers support static-mode collection as well as dynamic modes which require concurrent collection and transmission to the host and a gated dynamic mode for when two collection epochs within the heart cycle are required.

Discriminators and encoders are gantry-mounted for efficient utilization of space and minimization of critical timing signal pathways. TAC-ADC modules, view-plane processors, host-computer interface and monitoring electronics are rack mounted in close proximity to the gantry.

The discriminators and encoders have been designed, fabricated and tested. Three candidate ADCs have been evaluated and the selected unit is currently being tested with our prototype TAC. Design of the view-plane processor is nearly complete and critical components have been breadboarded and tested using the AMD System 29 microprogramming system development unit (F-1). System packaging and host computer interfacing design tasks are in progress.

B-15. Study of Block-Banded Toeplitz Matrices That Occur in a Time-of-Flight Tomography Algorithm

Personnel: N. C. Cheng, BCL
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Support: RR 00396

In (PR 16, B-11) we reported an image-reconstruction algorithm for most-likely-position data in time-of-flight tomography that can be described by a linear equation

$$\underline{\hat{\lambda}} = \underline{A}^{-1}\underline{n}/N_t,$$

where $\underline{\hat{\lambda}}$ is a vector representing the maximum-likelihood estimate of the image parameters and $\underline{n}$ is a vector containing the histogram data in the most-likely-position array. Both $\underline{n}$ and $\underline{\hat{\lambda}}$ are in lexical order and have dimension $M^2 \times 1$. The matrix $\underline{A}$ is an $M^2 \times M^2$ block-banded Toeplitz matrix and mathematically has the following property:

$$A_{(i,j),(m,n)} = \begin{cases} \alpha^{|i-j|,\ |m-n|} & \text{for } |i-j| \leq p \text{ and } |m-n| \leq p \\ 0 & \text{otherwise} \end{cases}$$

for i, j, m, n = 1, ..., M. Here, (m,n) represents the block indices and (i,j) the indices within a block, and p determines the number of nonzero elements in a block.

There are counts recorded outside the boundary of an image array even though the actual radioactivity is confined within the array. The dimension of the count array is L × L, where L equals (M + 2p) and the total number of counts $N_t$ includes the counts outside the image boundary. Studies have shown that the linear system can be rewritten as:

$$\underline{\hat{\lambda}} = \underline{H}_0^{-1}\ \underline{n}'/N_t,$$

where $\underline{H}_0$ is diagonalizable by a sine transform, and $\underline{n}'$ is a modified count array which is formed by folding back the four sides of the count array along the image boundary and subtracting them from the counts that are within the boundary.

Because of the highly structured nature of $\underline{H}_0$, its eigenvalues can be evaluated by first calculating the sub-block eigenvalues of (p+1) blocks and then the eigenvalues of a matrix formed by these sub-block eigenvalues. This procedure requires storage of $\{(p+1)(p+2)/2 + M(M+1)/2 + M(p+1) + M^2\}$ real words and could use M(M+1)/2 less words at the expense of much longer

execution time. For an image of 128 × 128 pixels, a minimum of 18K real words are needed.

The inverse of $\underline{H}_0$ is also highly structured. It is proven that $\underline{H}_0^{-1}$ is both block persymmetric and persymmetric within each block. Mathematically:

$$\underline{H}_0^{-1}(i,j),(m,n) = \underline{H}_0^{-1}(M+1-j,\ M+1-i),\ (M+1-n,\ M+1-m).$$

The reconstruction is implemented in the sine-transform domain:

$$\underline{Z}\,\hat{\underline{\lambda}} = \text{Diag}\left(\frac{1}{\rho_1}, \ldots, \frac{1}{\rho_{M^2}}\right) \underline{Z}\,\underline{n}'/N_t,$$

where $\rho_i$ are eigenvalues of $\underline{H}_0$ and $\underline{Z}$ is the sine-transform matrix. We found that there exists a decomposable fast sine/cosine transform based on the following equations:

$$S(2\ell) = \sum_{k=1}^{\frac{N}{2}-1} \rho_k^{\ell} \sin\frac{\ell k\pi}{(N/2)}, \qquad \text{for } \ell = 1, \ldots, \left(\frac{N}{2}-1\right),$$

$$S(2\ell-1) = \sum_{k=1}^{\frac{N}{2}-1} \alpha_k^{\ell} \sin\frac{\ell k\pi}{(N/2)} + \sum_{k=1}^{\frac{N}{2}} \beta_k^{\ell} \cos\frac{\ell k\pi}{(N/2)},$$

$$C(2\ell) = \sum_{k=1}^{\frac{N}{2}} \alpha_k^{\ell} \cos\frac{\ell k\pi}{(N/2)}, \qquad \text{for } \ell=1, \ldots, \frac{N}{2},$$

$$C(2\ell-1) = \sum_{k=1}^{\frac{N}{2}-1} -\beta_k^{\ell} \sin\frac{\ell k\pi}{(N/2)} + \sum_{k=1}^{\frac{N}{2}} \alpha_k^{\ell} \cos\frac{\ell k\pi}{(N/2)},$$

where $\rho_k^{\ell} = X_k + (-1)^{\ell} X_{k+N/2}$,

$$\alpha_k^{\ell} = X_k \cos\frac{k\pi}{N} - (-1)^{\ell} X_{k+N/2} \sin\frac{k\pi}{N},$$

$$\beta_k^{\ell} = -X_k \sin\frac{k\pi}{N} - (-1)^{\ell} X_{k+N/2} \cos\frac{k\pi}{N},$$

and where $S(\cdot)$ and $C(\cdot)$ are the sine and cosine transforms of the sequence $X(\cdot)$.

The elements in matrix $\underline{A}$ are defined as:

$$a_{(i,j),(m,n)} = \frac{N(i,j,m,n)}{N(i,i,m,m)} f(|i-j|, |m-n|),$$

where $N(i,j,m,n)$ is the number of coincidence lines that pass through both pixels indexed by $(i,m)$ and $(j,n)$. A simulation program that evaluates $N(i,j,m,n)$ for a system with a wobbling detector ring indicates that the ratio $N(i,j,m,n)/N(i,i,m,m)$ is not globally space-invariant. Geometric distortion may occur especially near edges of the image if the non-uniformity of the ratio is severe. One way of handling this problem is to divide the image into small blocks and process each block using different values of $\alpha_{(i,j),(m,n)}$. The error involved in block processing can be reduced by considering the problem of reconstructing an image with pre-determined boundary conditions. It is shown that

$$\hat{\underline{\lambda}} = \underline{H}_0^{-1} \underline{n}'/N_t + \hat{\underline{\lambda}}_c,$$

$$\underline{n} = \underline{n} - \underline{G}\,\underline{b},$$

and

$$\hat{\underline{\lambda}}_c = \underline{D}\,\underline{n},$$

where $\underline{b}$ contains the pre-determined boundary values around the image block, and $\underline{G}$ and $\underline{D}$ are pre-evaluated matrices.

1. A. K. Jain, "An Operator Factorization Method for Restoration of Blurred Images," IEEE Transactions on Computers, vol. C-26, pp. 1061-1071, November 1977.

2. A. K. Jain, "Fast Inversion of Banded Toeplitz Matrices by Circular Decompositions," IEEE Transactions on Acoustics, Speech and Signal Processing, vol. ASSP-26, no. 2, pp. 121-126, April 1978.

3. S. Zohar, "Toeplitz Matrix Inversion: The Algorithm of W. F. Trench," Journal of the Association for Computing Machinery, vol. 16, no. 4, pp. 592-601, October 1969.

4. N. C. Cheng, "Image Reconstruction Technique for Positron Emission System with Measurement of Time-Difference Information," Proceedings of the Eighteenth Annual Rocky Mountain Bioengineering Symposium and Eighteenth Instrumentation Symposium, vol. 17, pp. 27-33, April 1981.

## B-16. Resolution in Time-of-Flight Tomography Systems

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Support: RR 00396

The impulse response of an image-reconstruction system has been widely used as a measure of its resolution.[1] We have studied the effect of finite beam-width and finite bandwidth on the resolution of a tomography system employing time-of-flight measurements.

The probability density of position errors in time-of-flight measurements is an asymmetric, two-dimensional Gaussian function,[2,3] but in most mathematical models the uncertainty along the direction perpendicular to the coincidence line is ignored. When the ratio of beam-width uncertainty to TOF uncertainty is small, the reconstructed point source based on this simplified model is a two-dimensional Gaussian function with standard deviation that is 71% of that of beam-width uncertainty. For a practical value of beam-width uncertainty of 1.2 cm FWHM, the reconstructed point source has a FWHM equaling 0.85 cm. This is the limiting resolution when finite beam-width is ignored in the reconstruction filter. The result holds for both the "confidence-weighted array" and the "most-likely-position array" described by Snyder, Thomas, and Ter-Pogossian.[3]

The frequency response of reconstruction filters for the "confidence-weighted array" and the "most-likely-position array" are increasing functions of frequency. In practice, this response would be weighted by a low-pass "window" filter. When finite beam-width is included in the reconstruction

filter, the spectrum of the reconstructed point source will be that of the low-pass filter. For a circularly symmetrical filter of the form $J_1(2\pi r_o \rho)/\rho$, where $J_1(\cdot)$ is a Bessel function of the first kind order one, a point source is reconstructed as a cylinder with radius equal to $r_o$.

In most reconstruction algorithms, the beam width is ignored, and a low-pass window filter is used. The combined effect of finite beam-width and finite bandwidth can be expressed as:

$$\hat{\lambda}(r)=(2/\sigma_b^2)\exp(-r^2/2\sigma_b^2)\int_0^\infty \exp(-\alpha^2/2\sigma_b^2) I_0(2r\alpha/\sigma_b^2) t(\alpha)\alpha d\alpha$$

where $\hat{\lambda}(\cdot)$ is the reconstructed point source, $t(\cdot)$ is the inverse transform of a circularly symmetric window filter, $I_0(\cdot)$ is the modified Bessel function of zero order, and $\sigma_b$ is the standard deviation of beam-width uncertainty. For almost all the low-pass filters that are used in reconstruction algorithms, no closed form of this expression can be found, and it has to be evaluated numerically.

When the beam-width uncertainty is relatively small compared to the time-of-flight uncertainty, the degradation in resolution due to finite beam-width can be reduced by a two-step filtering. In the first step, the preimage is filtered as if the beam width were zero and in the second step, the reconstructed image is filtered with $\exp(\pi^2\sigma_b^2\rho^2)$, where $\rho$ is the radial frequency component. The low pass filter used in the first step has a dominant effect on the resolution of the final image.

Resolution is strongly dependent on the low-pass filter chosen for the reconstruction algorithm. There are two major factors in determining the bandwidth of this filter, namely, the sampling rate and noise power presented in the measurements. These two issues deserve further investigation.

Most of the well publicized algorithms used in conventional tomography reconstruction, such as the Shepp/Logan algorithm and the Lakshminarayanan algorithm, have disregarded the beam width, and they differ mainly in the choice of low-pass filters to accommodate different requirements of resolution and noise reduction. Resolution in time-of-flight tomography is affected by finite beam-width and finite bandwidth in a way that is similar to that in tomography without time-of-flight data.

1. G. H. Glover and R. L. Eisner, "Theoretical Resolution of Computed Tomography Systems," Journal of Computer Assisted Tomography, vol. 3, no. 1, pp. 85-91, February 1979.

2. N. A. Mullani, J. Markham, and M. M. Ter-Pogossian, "Feasibility of Time-of-Flight Reconstruction in Positron Emission Tomography," Journal of Nuclear Medicine, vol. 21, no. 11, pp. 1095-1097, November 1980.

3. D . L. Snyder, L. J. Thomas, Jr., and M. M. Ter-Pogossian, "A Mathematical Model for Positron-Emission Tomography Systems Having Time-of-Flight Measurements," IEEE Transactions on Nuclear Science, vol. NS-28, no. 3, pp. 3575-3583, June 1981.

B-17. A Mathematical Model for Emission Tomography Systems Having Time-of-Flight Measurements

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L. J. Thomas, Jr., BCL

Support: RR 00396
HL 13851
HL 25944
ENG 76-11565

A mathematical model describing the dominant effects in an emission tomography system having time-of-flight measurements has been developed. This model includes the fluctuation statistics associated with positron annihilations and the error statistics associated with finite detector-resolution and finite propagation-time measurements. The model is useful for identifying reconstruction algorithms and their performance when time-of-flight measurements are available. Details of the model have been published.[1]

1. D. L. Snyder, L. J. Thomas, Jr. and M. M. Ter-Pogossian, "A Mathematical Model for Positron-Emission Tomography Systems Having Time-of-Flight Measurements," IEEE Transactions on Nuclear Science, vol. NS-28, no. 3, pp. 3575-3583, June 1981.

B-18. Signal-to-Noise Ratio in Time-of-Flight Tomography

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The signal-to-noise ratio at each location in a reconstructed image is one measure of the performance of an emission tomography system having time-of-flight measurements. This ratio depends on many aspects of such a system including the choice of data to be acquired for subsequent processing and the algorithm used in the subsequent processing. We have used the mathematical model described in (B-17) to predict the signal-to-noise ratio for two data-collection arrays that might be adopted, called the "confidence-weighted" and "most-likely-position" arrays. For each data array, we assume that the processing is selected to produce the maximum-likelihood estimate of the radioactivity. As an example, the noise performance has been studied for a distribution of activity that is uniform over a circle of radius 15 cm (see reference 1 of B-17). For this example, we find that the confidence-weighted array has the greater signal-to-noise ratio. Other examples are being investigated.

B-19. Effects of Quantization of Time-of-Flight Measurements in PETT

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Support: RR 00396
HL 25944

We have initiated an effort to predict the signal-to-noise ratio (SNR) performance in positron-emission tomography as a function of the number of levels used in quantizing the time-of-flight measurement. We have achieved preliminary results based upon some mathematical approximations. These results indicate that for a specific image example there is a 0.06 dB degradation in SNR due to five bits of quantization. The example used is the same as that for SNR calculations derived in [1] with a "confidence-weighted" pre-image and a time-of-flight measurement-error distribution of 6.75 cm FWHM.

Efforts have shown that analytical verification of the approximations is non-trivial. For this reason alternative approaches to modeling the problem are being investigated.

1. D. L. Snyder, L. J. Thomas, Jr., and M. M. Ter-Pogossian, "A Mathematical Model for Positron-Emission Tomography Systems Having Time-of-Flight Measurements," IEEE Transactions on Nuclear Science, vol. NS-28, no. 3, pp. 3575-3583, June 1981.

C. Systems for Specialized Biomedical Studies

In previous reports, activities in this section were considered in the contexts of pathophysiology and CNS studies. The broadening of scope implied by the new title reflects an engineering trend where diverse problems are solved by methods having much in common.

The image acquisition system proposed (PR 16, G-10) for DNA restriction mapping is closer to reality with the recent introduction of new light sensitive arrays. At a more theoretical level, models of DNA base pairs have been developed which are amenable to computer-based statistical analysis.

As in previous years there has been much emphasis on the techniques of image processing in various forms. Following a number of improvements and additions both to hardware and software, the second version of a microscope based imaging instrument for autoradiographs is now operational. Silver grains can be detected and counted at rates which suggest that the instrument will have wide general utility. The relative simplicity of the hardware combined with carefully developed and expandable software makes it likely that it will find application in other areas of biomedicine where automatic counting and sizing are desirable.

Three activities in this section are concerned with vision and ophthalmology. Development continues on the constant-area applanation tonograph (PR 16, G-2) and a database of normal and abnormal tonograms is being developed rapidly.

The database relating visual field abnormalities and the presence of occular hypertension (PR 16, G-4) has also been greatly extended and is now sufficiently large to permit clinical generalizations to be made about the progressive loss of vision which accompanies glaucoma. Work is also proceeding on perimetric studies where color rather than contrast is the variable under study. There is evidence to suggest that this may be a more sensitive technique for determination of incipient glaucoma. System development and evaluation of this technology will continue in the coming year.

An attempt is being made to re-activate topological analyses of the EEG to test the hypothesis that the information content of this signal lies not so much in its steady state characteristics but rather in the somewhat subtle rhythmic changes that can be observed by multichannel topography.

In summary, the major activities of this section are, and will continue to be, concerned with the transduction, transformation and display of physiological variables.

## C-1. An Automated Autoradiographic Analysis System for Neuroanatomical Studies

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NS 15070

A previously described (PR 15, F-4; PR 16, F-4) second-generation microscopy-based instrument for high-speed automatic quantification of neuroanatomical autoradiographs has been essentially completed. During the past year work was concentrated on system integration and software development. In addition, modifications have been made resulting from experiences gained as the instrument underwent its first trials with users.

Several new commands have been added to the repertoire of the automatic stage controller (ASC). Three commands (SETX, SETY, SETZ) allow independent changes to each of the microscope stage coordinates.

The operator control panel (OCP) has been completed. Debugging and testing of its 6802 software followed operational verification of hardware. Modifications to permit easier control of the microscope stage via the OCP joystick were made, as were improvements in the OCP message display optics and software.

Considerable progress was made in integrating the video processor and image analyzer (VPIA). The VPIA consists of a General Electric TN 2500 CID solid-state camera with 8-bit digital outputs, a Lexidata 3400 image and graphics processor, an LSI 11/2 microcomputer to interpret commands from the system supervising processor to the VPIA and appropriate interfacing hardware.

Since the manufacturer of the image processor did not supply an interface to the LSI 11's Q-BUS, a DMA-type interface was constructed and an RT-11 driver program written to allow convenient high-level language utilization of the Lexidata. Since the driver is compatible with the one supplied by Lexidata for use with PDP-11 computers, software developed on these machines (F-4) was immediately usable.

Detailed analysis of the Lexidata's operational speeds revealed that the standard 16-bit host I/O port through which it communicated with the LSI 11 was not capable of handling data from the TN 2500 camera in real time, despite claims to the contrary. Subsequently, the Lexidata was retrofitted with a higher speed "second input port," and a line-buffer interface

constructed to match the TN 2500 to the second port. The interface allows an entire 240 × 240 pixel image to be acquired in two video fields (1/15 second). The system may also be operated in a serial "movie" mode, providing a 15 frame/second television like display of the digital data from the camera.

Software development for the video processor included the writing of a RATFOR program, VIDMON to supervise the VPIA hardware, interpret and respond to commands received over the IEEE-488 bus, and invoke Lexidata microprograms. In addition, microprograms to perform automatic threshold selection, autofocus criteria generation, and grain counting were written and debugged.

The last element of the system to be developed was the supervisory processor executive program, SUPER. Like VIDMON, SUPER is written in RATFOR. It is responsible for coordinating the operations of the VPIA, ASC, and OCP, implementing the machine's operational protocol, and interacting with the user via the OCP. SUPER makes extensive use of the Digital Equipment Corporation (DEC) IEEE-488 instrument bus subroutine library, since all interaction with other modules in the system occurs over the IEEE bus.

Since the SUPER program evolved from a collection of test routines used during the debug phase, a more polished version of the supervisory executive will be delivered. The new executive could also incorporate modifications suggested by the user community. For this reason, a detailed design specification for a new executive was written, and work is progressing on writing the software.

A series of preliminary performance evaluations has been initiated, the results of which indicate that the instrument's performance meets design expectations in most respects. Peak grain counting speeds of up to two fields a second are possible, with accuracies on the order of $\pm$ 8%. Experience with the auto-threshold and auto-focus algorithms has revealed good performance with the former and excellent performance with the latter. Work is underway to install an improved auto-threshold algorithm with less tendency to choose an incorrect threshold for low contrast images with few silver grains. In addition, a new algorithm which will correctly detect silver grains of diverse shape is under development.

Presentation of results from the grain counter is done primarily through pseudocolor and gray-scale grain-density maps; a sample is shown in Figure 1. The density maps are produced by an Image Resource Videoprint 3400 in color or black and white on Polaroid or 35 mm film. The Videoprint 3400 is one of the first relatively low cost, high-quality color hardcopy devices to appear on the market.

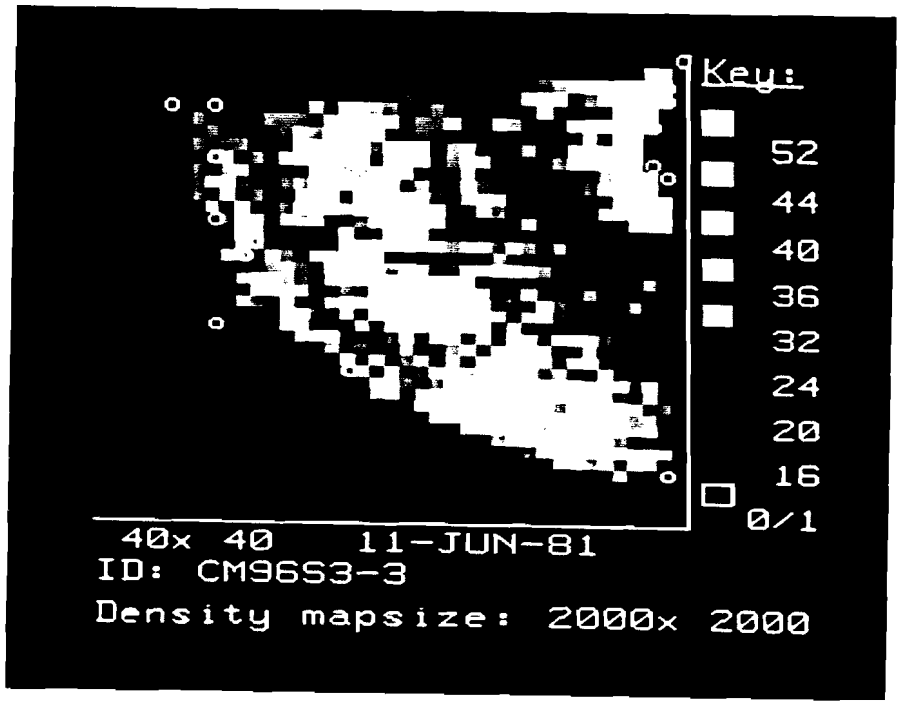


Figure 1. Sample grain-density map. Whiter regions indicate more intense labelling. White circles represent morphological landmarks which help to correlate the grain-density map with underlying tissue structures.

## C-2. DNA Restriction-Mapping Studies

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J. S. Massey, BCL
M. V. Olson, Ph.D., Genetics

Support: RR 00396
GM 28232

The objective of this activity is to develop a global approach for constructing restriction mappings of eukaryotic DNA. The project is currently focusing upon the yeast genome since yeast has the most extensive genetic map of any eukaryotic organism and has a transformation system which offers the best general method of correlating the physical and genetic maps.

The project could be expected to lead directly to new knowledge about the global topology of genomic DNA and the sequence dependence of recombination; it could also pave the way towards detailed studies of such topics as the organization of transcribed and non-transcribed regions, the genomic distribution of repeated elements and the DNA sequences associated with centromeres and teleomeres. The resultant library of cloned segments of yeast DNA sequences will be precisely catalogued with respect to the genomic origins of each clone.

A preliminary image-acquisition experiment with a solid-state video camera described in the previous progress report (PR 16, G-10) indicated that a 1024 linear array would suffice and, accordingly, was purchased from RETICON with appropriate electronic control circuitry. A program entitled DNASCN[1] was written in RATFOR to facilitate the storage, retrieval and manipulation of image vectors obtained from the linear array. Experiments were performed on the electrical and optical properties of the array to study 2048- and a 1024-point spacing. It was concluded that a 1024 array would perform the image acquisition with sufficient resolution.

During the year, new image-acquisition systems were introduced by EIKONIX, OPTRONICS and Cambridge Instruments. A preliminary study of these image acquisition systems showed that they could be used to perform the gel scanning. It is now proposed that one of these units be purchased and that it be interfaced with an LSI-11 microcomputer for data acquisition and fragment size analysis. It is further proposed that system software be developed which would allow computer-assisted editing of the results, preprocessing of the fragment lengths and order information, and the transmission of this information in machine-readable form for topologic analysis by computer.

To aid in the reconstruction of the genome from the clone data, a probabilistic model of the DNA base pairs was developed. Based upon experimental evidence, the fragment lengths are assumed to be exponentially distributed. It is futher assumed that these fragments are distributed independently of each other. This model has been useful in three areas.

First, the success of the experiment depends upon a random sampling of the genome. Any bias in the sampling will tend to leave gaps in the reconstructed genome. It was proposed to use a 6-base-pair restriction enzyme R1 with partial digestion to create the pool of segments of DNA to be randomly sampled for cloning. Using the proposed random genome model, it was found that the longer the partial digestion, the more the pool of cloning samples became biased towards those segments with fewer fragments. Preliminary experimental results obtained in Dr. Olson's laboratory have tended to confirm this observation. By using a 4-base-pair restriction enzyme, there should be substantially less biasing of the cloning sample pools; this has been observed experimentally. This method will be used to generate the pool of clones in the future.

Secondly, the random genome model has been used to determine the potential distribution of the fragments in a segment of 20K base pairs, the length of the cloning vector. A sample of 100 cloned samples is

currently being prepared. This sample will be used to determine the extent to which the fragments are independent of each other. Another experiment is also currently in progress to confirm the assumption about the exponential distribution of the fragment lengths. These two experiments will determine how well this simple model matches the yeast genome.

The fundamental problem in the eventual reconstruction of the genome from the fragments is determining when two clones overlap and to what extent. A preliminary investigation was made using the random genome model and a measurement accuracy model which included linear and geometric measurement errors. The probability that two randomly chosen genomes appear to overlap in K positions was determined for several situations. It was determined that information about the order of fragments within the clone was very useful. It is proposed to continue to develop the random genome model to aid in the overall reconstructability of the genome from the clone data.

1. J. A. Esrig, "DNASCN - Gel Data Manipulation System," BCL Working Note No. 13, July 20, 1981.

## C-3. Constant Area Tonometry System

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Support: RR 00396
EY 00256

The constant-area applanation tonometry studies have continued this year (PR 16, C-2). These collaborative studies, involving researchers from the Department of Ophthalmology and BCL, have resulted in the acquisition of more than three hundred eighty tonograms. During each experiment, the tonograms were recorded on a strip chart and stored on a diskette using the universal storage device (PR 16, G-3).

Recent work has focused on the analysis of the tonograms in order to identify and correlate characteristic tonographic features with physiologic causes. Preliminary results have been reported[1] and the tonographic features may ultimately provide clinically useful diagnostic information. To aid in evaluating this possibility, files detailing the ocular history of each participating subject are being developed. Tonograms will continue to be acquired and analyzed in the laboratory to build a database from which meaningful correlations can be drawn.

1. R. A. Moses, R. J. Arnzen, and W. Grodzki, "Constant Area Applanation Tonography," Journal of Investigative Ophthalmology, in press.

C-4. Visual Fields and Ocular Hypertension

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Support: RR 00396
EY 00336
EY 02044

A graphic database has been assembled, containing the visual-field records of patients being treated for glaucoma and ocular hypertension. The glaucoma registry at the Department of Ophthalmology contains the records of 2,462 patients. Of these, 251 carry the diagnosis of glaucoma and 826 have been classified as having ocular hypertension (i.e., those patients distinguished from those with glaucoma by virtue of having elevated intraocular pressures but normal visual fields). The visual-field records of these patients have been selectively abstracted into a graphic database, using a PDP-11 minicomputer system as previously described (PR 15, C-4). Preference has been given to those records that cover the longest chronological periods. Seventy three patients with glaucoma have been continuously observed for 10 or more years, and an additional 52 have been followed for between 5 and 10 years. Particular interest has been given to the morphological patterns of visual field defects of patients with glaucoma at the time of earliest detectable lesions. A total of 98 eyes in 72 patients was shown to have developed initial defects while under continuous observation. The patterns of defects found in these eyes will be used to predict the most probable locations of future defects in the eyes of patients with ocular hypertension. In addition, certain characteristic patterns of chronological development have become evident. In 22 of the eyes that developed initial defects these were found to be transient. Defects that were transient, however, were consistently shown to reappear at the same site as their initial appearance and to be denser defects at the time of their reappearance. In those eyes whose initial defects were not transient, a rapid progression of visual loss was observed, occurring within a period of 1 year or less. Subsequent follow-up for additional periods of 8 to 10 years in these eyes showed a remarkable stability (non-progression) of visual field defects. This has suggested that: the natural history of visual loss in glaucoma is characterized initially by a fluctuating state during which a defect may or may not be demonstrable, and that those patients in whom initial defects appeared to progress rapidly may have been detected late in this initial period of threshold damage. The earliest defects during this threshold period tend to be relatively subtle and difficult to detect by standard techniques of kinetic perimetry. The use of statically presented targets positioned over contiguous areas of the visual field (where these defects are most likely to be discovered) is probably the most sensitive technique for detection. The visual-field data-acquisition system, described in (PR 15, C-3), has been a reliable and convenient tool for acquiring both static and kinetic visual field data. The same system used for the graphic database has also

been used to generate 3-dimensional graphic images of display surfaces that represent data obtained from static perimetric examinations, thus allowing the use of point patterns that maximize the likelihood of detection of early glaucomatous visual field defects.

## C-5. Color Perimetry Studies

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EY 00336
EY 02044

Since visual system damage seems to occur in patients with glaucoma in a subtle or threshold fashion (C-4), such that it is not initially detectable by ordinary light-sense (brightness) perimetry, and since color vision defects are often demonstrable in glaucoma patients, using foveal tests of color vision, a technique is being devised to allow visual field examinations based on determinations of chromatic rather than brightness thresholds. It is suspected that visual field defects mapped in this fashion may provide a more sensitive means of detecting and monitoring visual loss in patients with glaucoma. A microprocessor based instrumentation system for generating images on a color television screen is being developed to allow a form of constant-brightness, color-contrast perimetry to be performed. Work done over the past year, using a prototype color-video module reported in PR 16, C-5, has established that brightness matching of heterochromatic target-background combinations can be achieved using a form of flicker photometry, and that these brightness matches are uniform over the entire central visual field. The brightness matches thus obtained have also been shown to obey predictions of algebraic brightness additivity. Thus, chromatic targets can be brightness-matched to a neutral gray surround at one location in the central visual field, following which an entire family of test targets can be produced that vary only in level of chromatic saturration, while remaining equi-luminescent. In this manner the visual field should be open to exploration with a purely chromatic visual function, since all brightness clues to target detection will have been eliminated.

A color perimetry system which includes the prototype color-video module, a Motorola Exorset 30 and a photometer is being configured to provide a clinical tool for exploring chromatic visual fields. Background, target and fixation images are displayed on a color-video monitor under the control

of an Exorset 30. Programs for calibrating the luminance of the video screen using a calibrated photometer have been written. User control of the system is accomplished by interacting with the Exorset 30 console. The system components communicate over the standard IEEE-488 instrumentation bus. Plans are to continue the development of the color perimetry system for use in the visual field studies.

## C-6. Data Acquisition System for Extracellular Cardiac Potentials

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Support: RR 00396
American Heart Association, Missouri Affiliate, Inc.
Buder Peters Scholar Award

During the past year the data acquisition system described in PR 16, C-6 has been upgraded to increase its utility in electrophysiological studies. A new set of software routines was written to permit more flexible data acquisition. With these changes it is possible to review the status of all active signal-processing modules (SPM). Changes to specific parameters in selected modules can be made as needed without reinitializing the system as was required by the previous software. In addition, the new software includes features which permit the operator to verify the detection and timing of pacemaker pulses and to verify the functioning of the analog sampling modules and disk drive prior to initiating data acquisition. The system now displays, on-line, the current disk track and sector while data are being acquired. These features have provided improved reliability of data collection and the ability to easily adapt sampling protocols to changing physiologic conditions.

A second addition to the system which has enhanced its usefulness is the incorporation of a signal-generation module (SGM). The SGM is programmed to reconstruct two selected analog signals for display on an oscilloscope. This provides visual confirmation of the data being acquired.

A number of clinical studies using electrophysiology data collected by the system have been performed. These include studies to investigate the reproducibility of single-stage coronary artery occlusions following an initial "scout" occlusion, differences between the "scout" occlusion and subsequent occlusions, differences between single stage and two-stage occlusions, and the effect of sympathetic stimulation on electrogram

characteristics. Preliminary analysis of the single stage vs. two-stage data indicates no significant differences in the electrograms despite significant differences in the associated regional blood flow.

The data collected from the present acquisition system are being studied to resolve signal acquisition and data compression issues for long-term chronic recordings. An initial study is being performed on the spectral properties of the electrograms. It is hoped that this investigation will yield results on appropriate sampling rates for data collected during various experimental interventions. Preliminary results show spectral components with a maximum frequency ranging from 500 Hz to 1500 Hz. Future studies on the statistical properties of the data are planned. The purpose of these studies will be to investigate various coding and data-compression schemes.

In order to increase the data storage capacity of the system, two 5-Mbyte microwinchester disk drives with controllers have been purchased. Plans are for one rigid disk to become the primary data acquisition device for the system and the other to serve as a backup. The floppy disk drive will then be used for backup storage and for data transfer to the data analysis system. The drives and controllers are currently undergoing evaluation (F-5).

## C-7. Development of a Toposcopic Display System for Electroencephalography

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Support: RR 00396
RR 07054

During the past few years there has been a resurgence of interest in toposcopic display techniques for electroencephalography. These take advantage of modern computer technology and fall into two basic categories: there are those which display contours (similar to those pioneered by Rémond) and those which take frequency transforms of the signals over a period of some seconds and display them, often in color[1] on a projection of the head. Summaries of topographic methods have been published.[2,3] Contour techniques require the construction of a large number of maps if changes in distribution are to be studied whilst frequency transform methods inevitably involve integration over several seconds. The frequency selective toposcope[4,5] which was a powerful tool for the study of the intrinsic rhythms of the brain has not been duplicated and has not found wide use on account of the extreme complexity of the analog hardware involved. The present note details a method by which the Walter-Shipton device can be inexpensively and reliably produced using modern digital technology. Any standard

oscilloscope which has X-Y inputs and provision for intensity modulation can be used as the display. This instrument differs from those previously described in that the image is stationary and can be retained indefinitely: photographs or other hard copies are required only for those records which are to be permanently filed.

Inexpensive CMOS logic is used. Although the instrument described here has only 9 channels, up to 16 channels can be implemented in this logic family; extension to 32 channels is possible using faster devices. A block diagram is shown in Figure 1. Signals are amplified and fed to analog/digital (A/D) converters which load a memory system. A single static memory element (1024 × 4 bits) is used for each channel. In the current version, signals are sampled at 80 s/s giving an effective bandwidth of approximately 30 Hz. This is sufficient for the study of alpha and beta activity. Because the system is not primarily an amplitude indicator it has been found sufficient to digitize the input signal to four bits, i.e. 16 levels. Signals may be obtained directly from EEG amplifiers or from a multi-channel tape recorder. The display is available as soon as 1024 samples have been obtained (i.e. in 12.8 seconds) which is the maximum epoch length which can be studied on line. Separate A/D converters are used, multiplexing was eschewed since stroboscopic artifacts would be produced by the multiplexer clock; similar artifacts have confused the interpretation of a number of toposcopes. When full, the memories are read and continuously cycled at high speed, the actual rate being under operator control, and their outputs converted to analog form. As the circles are moved by the X and Y decoders, one of the data streams is chosen by the channel selector and this output forms the "Z" (or brightness) input to the oscilloscope.

The concentric circles which form the basic Walter-Shipton display are produced at approximately 9 Hz. A function generator (ICL 8038) produces a sine wave which is fed to a balanced modulator IC2. At each zero crossing of the sine wave a D/A converter is advanced by one count and the resulting staircase waveform used as the multiplicand in IC2. Thus a balanced, step-modulated sine wave is produced which, after appropriate phase shifting, produces the concentric circular display on the face of the cathode ray tube. When 32 circles have been displayed a second counter (IC4) advances and its contents are decoded into x,y, components by a pair of 14016 quad analog switches and appropriate resistors. The position of the circles on the oscilloscope screen is determined by the output of this network. By appropriate selection of the decoder parameters their centers can be made to correspond to the electrode positions. The 9 Hz rate is sufficient to ensure that the whole frame repeats 30 times per second producing a stable image, free from flicker. The memory contents which are read out at variable speed, form the Z axis signal to the cathode ray tube so that the display contains a stationary pattern akin to that of the original toposcope. The display can be viewed for as long as required or photographed. An advantage over the original machine is that data can be retained indefinitely in the memory and observed at a number of different sweep speeds. Design is complete and construction and testing are underway. Arrangements have been made with a number of EEG centers to evaluate the system using tape-recorded data.

1. F. H. Duffy, J. L. Burchfield, and C. T. Lombroso, "Brain Electrical Activity Mapping (BEAM): A New Method for Extending the Clinical Utility of EEG and Evoked Potential Data," Annals of Neurology, vol. 5, pp. 309-321, 1979.

2. H. Petsche, in Handbook of EEG Technology, A. Rémond, ed., Elsevier, Amsterdam, vol. 5, part B, 5B-6, 5B-54, 1972.

3. R. Cooper, J. Osselton, and J. C. Shaw, in EEG Technology, 3rd edition, Butterworth, London, pp. 282-287, 1980.

4. W. G. Walter and H. W. Shipton, "A New Toposcopic Display System," Electroencephalography and Clinical Neurophysiology, vol. 3. pp. 281-292, 1951.

5. H. W. Shipton, "A New Frequency Selective Toposcope for Electroencephalography," Medical Electronics and Biological Engineering, vol. 1, pp. 483-395, 1963.

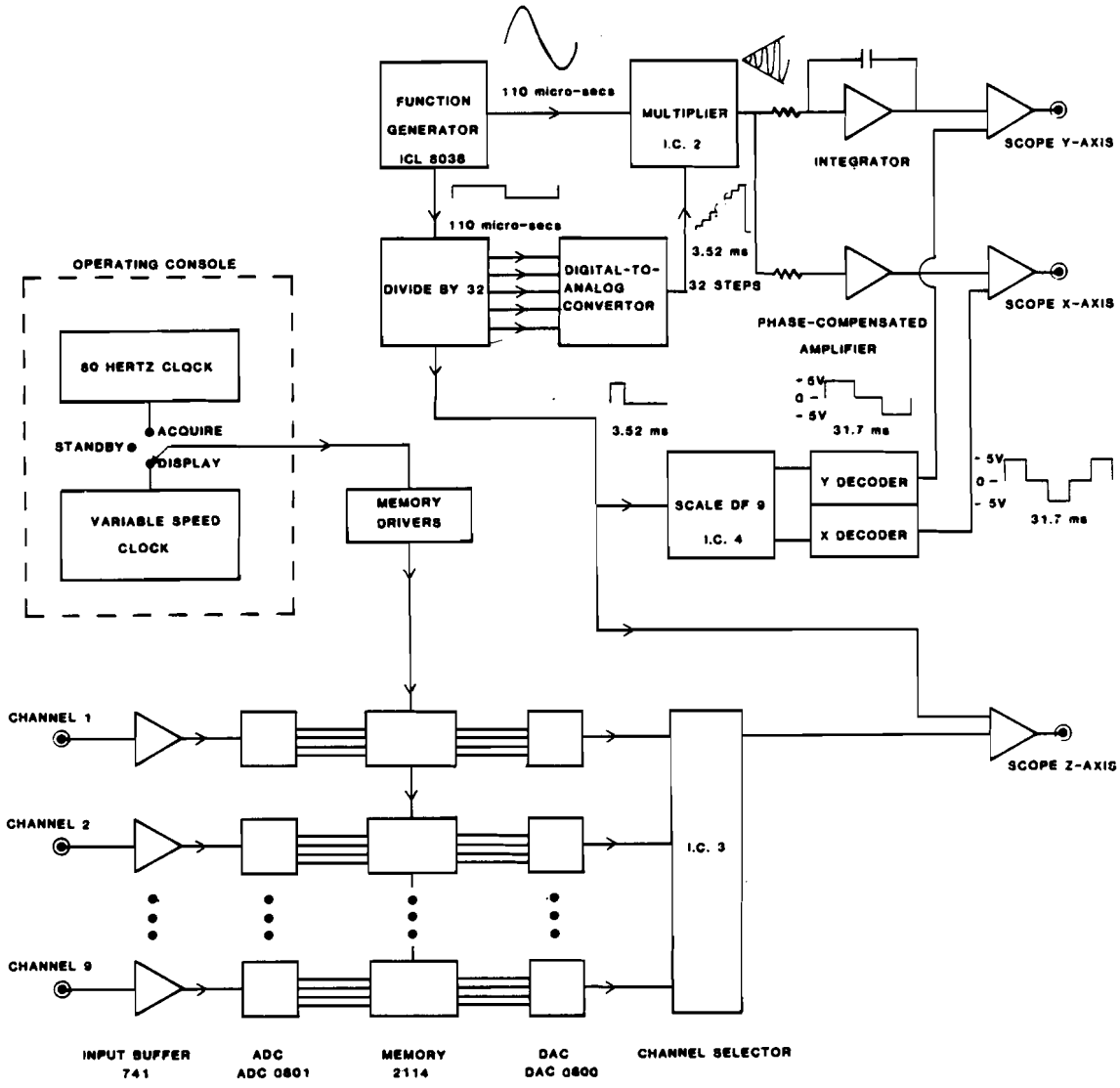


Figure 1. Simplified Block Diagram

## D. Database for Disease Management and Research

The need for database facilities in several BCL projects became compelling in the early 1970's. Prior experience underscored the desirability of interactive data entry in order to assure adequate quality and to provide easy access to up-to-date information. Primarily through external funding, a minicomputer-based system (MUMPS) capable of supporting database activities was imported, rewritten for the PC-1200, and applied in radiation oncology. This application has developed into an installation, the Oncology Data Center (ODC), located within the Mallinckrodt Institute of Radiology. BCL operated a MUMPS facility for training purposes and investigations into database characteristics until 1978. A fee-for-service installation, the Medical Computing Facilities (MCF), was organized within the Medical School to provide MUMPS service to those who do not desire to operate their own installations. On July 1, 1980 the Medical Computing Services Group (MCSG) was organized by the Computing Facilities to assist researchers with data-management requirements by providing access to both MCF's MUMPS system and to the University's IBM System/360-370. Prior activity in the Laboratory has included the development and operation of several information systems for the support of ongoing research projects. Almost all of these databases have concentrated on longitudinal information because of its importance to clinical investigations of chronic diseases.

The development and operation of such databases has been deemphasized as a research activity because such services can now be provided by service organizations. Database activities have centered on the development of a methodology for the design of composite medical-information systems capable of dynamic system evolution in response to user needs. A data model called Abstract Database System (ADS) has been defined which provides a framework for structuring information (D-1). The design methodology will be tested through the implementation of the Neonatology Database (D-2). Development activities directed toward this high-performance information system have been federated within the Information Systems Group, a sister resource group based in the Computer Science Department.

The Neonatology Database serves as a frame of reference for the development of the data model. The importance of the other databases reported here results from our goal that a medical-information system should allow for the amalgamation of separate databases in a way that is responsive to individual user views of shared data. These databases also provide concrete examples of medical-information needs and thus contribute to the relevance of model-development activities.

D-1. Information Systems Group

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Support: RR 00396
HS 03792
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The Information Systems Group provides the collaborative structure within which participants from the Department of Computer Science, the Computer Systems Laboratory, the School of Medicine, and the Biomedical Computer Laboratory are addressing the development of a methodology for the design of composite medical-information systems. The development activities can be divided into four major categories: model, design studies, implementation and Neonatology Database. The more theoretical portions of the work on a design methodology fall in the first category and the more applied tasks in the second. The design-studies category also includes architectural studies and custom LSI design experiments. Implementation activities are to establish an adaptable, experimental environment for the support of a trial implementation of a medical-information system designed according to the methodology specified by the Abstract Database System (ADS) data model. The Neonatology Database (D-2) undergirds the entire effort providing a relevant environment for testing concepts, models and implementations.

The tightly knit interdisciplinary team ensures an environment based on direct experience with the operation of a complex medical-information system which contains data on actual patients and which is used by clinically active decision-makers. Such an environment facilitates realistic model development and architectural considerations.

Properties of the data model (ADS) have been refined and extended through experience gained by trial application to the description of the MUMPS-based Neonatology Database and by implementation of an interpretive version of ADS on the DEC System 20. Several trial designs of an associative-memory subsystem component were carried out, and a custom LSI layout of one of these subsystems has been completed and is ready for fabrication. Implementation activities included initial steps toward an integrated

hardware/software development environment for the Motorola M68000 microprocessor. Software support now includes cross-assembly and cross-compilation for the "C" programming language. Specific details of these activities are summarized elsewhere.[1]

1. "A Medical Information Systems Design Methodology," HS 03792-03 Continuation Application, J. R. Cox, Jr., June 1981.

## D-2. Neonatology Database

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For medical personnel, day-to-day clinical exposure to sick newborns stimulates many questions based on historical, clinical, and/or laboratory data. The Neonatology Database (NDB) (PR 12, D-16; PR 13, D-5; PR 14, D-5; PR 15, D-5; PR 16, D-5) was designed to allow the easy formulation of queries and their rapid response. Admission data, including maternal history, perinatal history, immediate post-delivery data, and initial admission evaluation are gathered soon after an infant's admission. Disposition data are gathered at appropriate times during the hospitalization. A research nurse summarizes the in-hospital stay by recording problems, therapies, and procedures along with related complications, concurrent events, attributes, and features.

This MUMPS-based database has existed on three separate computer systems since its inception in June 1975. The database was first developed on an Artronix PC-1200 system as a pilot study to determine coding strategies. The stabilization of encoding techniques coincided with the decision to transfer to the more powerful Artronix MODULEX system in June 1977. The dissolution of Artronix, Inc. and subsequent operational problems with the MODULEX system necessitated the decision in June 1979, to transfer the entire 953-patient database to a Tandem system operated by the Pathology Department of St. Louis University. Since bit-map functions did not exist in this version of MUMPS, a different method for searching files was designed and implemented. The alternate searching method was satisfactory for temporary use, but it was unacceptable for long-term use. The author

of the local MUMPS interpreter was persuaded to incorporate bit functions and the system was redone. The system has been stable since December 1979 and new software has been developed to extend its use. The current patient population is 2453.

Important developments have included: 1) improving performance by utilizing bit functions for inverted-file manipulations, 2) redesigning the masterfile for time-modified queries, and 3) addressing data-integrity issues. Work in the current year can be summarized under four headings: 1) System Enhancements, 2) Queries Involving Temporal Relationships, 3) Data Integrity, and 4) Other Databases.

System Enhancements have included the development of a query-specification method which allows interaction in language more natural than the symbolism used previously. Users now may answer prompts by keying only enough of the desired term to avoid ambiguities. Other enhancements have been made to the various report generators and to the features which deal with quantitative data.

Queries Involving Temporal Relationships are required to address information acquired during hospitalizations which sometimes extend to two years. Most of these queries can be answered in one to two minutes and this performance has been acceptable to the system users. The maximal set of qualifying patients is obtained from the inverted file. Then, temporal constraints are checked by utilizing the patient master file. In the coming year the performance of these queries will be improved, related features will be enhanced, and the allowable complexity of the queries will be increased.

Data Integrity was addressed initially via consistency checks on individual items during data keying. Over the past two years we have concentrated on identifying inconsistencies among items. These checks are applied after data are keyed because the entire summary of a patient's course is required for comparisons. This process of data checking requires continuous monitoring by both the neonatologist and the database administrator. However, several benefits have been documented which include: 1) enforcing definitions, 2) preventing the erroneous repetition of information, 3) encouraging the input of attributes and modifiers, 4) reviewing admission data, 5) aiding the consistency in dating, 6) increasing the consistency between statements, and 7) providing a communication mechanism. The goal of the effort is to maximize the system's ability to define errors correctly and minimize human review.

Other Databases can be incorporated readily because the system provides a generalized format so the system's features can be transferred to other medical contexts. Two such databases have been developed: Mineral-Homeostasis and Mineralization Database (D-3) and Obstetrics Database (D-4). Another database concerning pediatric surgery was considered but this group was advised to utilize the services of MCSG. A desensitized copy of the Neonatology Database was sent to Rush-Presbyterian-St. Luke's Medical Center of Chicago to aid their development of a similar neonatal database.

The Neonatology Database provides an important frame of reference for the development of the data model called Abstract Database System (ADS). Certain features of this medical speciality, including the complexity of the data relationships, the attached time metric, and the two contexts involved (mother and infant), make the NDB especially attractive for evaluating the model. The NDB features exist in an application with a sufficient but not overwhelming number of patients. The MUMPS version of the NDB has been used to assess the value of associating a descriptor with each object in a database and to determine the impact that such comprehensive consistency checking will have on data collection. It has provided examples of relationships which can be handled with more and with less ease in an ADS implementation. As different ADS implementations of the NDB are defined, MUMPS programs will be written in order to assess the required number of elements, sets, assertions, and functions and also to tabulate other items of interest. Performance estimates can be made which will influence future enhancements to the model. These estimates will be compared with the current MUMPS implementation.

## D-3. Mineral-Homeostasis and Mineralization Database

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The Neonatology Database (D-2) provides a generalized format so that self-contained patient subsets can be established quickly in the database, a variety of tabulations and simple analyses can be performed, and data can be shared between files. The Mineral-Homeostatis and Mineralization Database served as the test case for this generalization of the system. Dr. Laura Hillman of St. Louis Children's Hospital is studying a subset of the population in the Neonatology Database as well as additional infants treated at the Barnes Hospital Premature Nursery. A total of 243 infants have been studied on a series of protocols to evaluate bone mineralization and calcium-phosphorous homeostasis.

Under the first protocol, 80 premature infants and 32 small-for-gestational-age (SGA) infants were studied serially at three-week intervals with X-rays and chemistries. Intakes and weight gains were recorded daily, and lengths and head circumferences were recorded weekly. Prenatal, neonatal, and hospital-course data were collected as well. Based on these data, new protocols for evaluating the effectiveness of therapeutic interventions are now employed. The infants are followed in a special

clinic where long-term follow-up data, including growth parameters, I.Q. testing, and dental evaluations will be collected and added to the database for comparison with clinical and research data.

The full value of the system will be realized for this application when complete admission, in-hospital, laboratory, and follow-up data have been entered for all infants included in the study. Keying of these data has continued over the past year, and two new data classes, in-hospital and follow-up, have been defined. All of these data are gathered and entered by a Pediatric Nurse Practitioner.

Because of this database, the components of the system which deal with data entry and analysis of quantitative data have improved. A pilot study on the entry of data via medical terms rather than via code numbers was conducted with this application. As a result of that study's outcome, this data-entry technique is now used for all applications. New time-frame calculations and statistical routines have been added for quantitative data. Parameters also can be derived from stored quantitative data. This application will make a major contribution to the development of methods for manipulating in-hospital data. In-hospital occurrences are summarized weekly rather than noted daily. Therefore, different types of queries for temporal relationships will be required for this database than for the Neonatology Database.

This database will aid the development of the ADS data model because of its emphasis on quantitative data, because of the different time metric utilized for in-hospital data, and because the data are collected under a research protocol.

## D-4. Obstetrics Database

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Support: HS 03792
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Another database has been defined this year which utilizes the generalized format provided by the Neonatology Database (D-2). The Department of Obstetrics and Gynecology at Washington University provides medical care during pregnancy and delivery to approximately 4,500 women annually. The magnitude of medical information generated on this number of patients has engendered a desire for more complete and accessible accounts on the variety of obstetrical conditions managed. The Department's

function as a referral center for the management of complicated pregnancies and deliveries further mandates an ongoing information system capable of assisting in monitoring changing therapies and procedures.

All deliveries performed at Barnes Hospital as of March 15, 1981 are recorded in the database. Data forms which are included in the patient's hospital chart are completed by the appropriate resident. These forms are reviewed by the obstetrician who heads the computer project, and then their contents are entered by a part-time clerk. Basically, the completion of the forms requires checking the appropriate item or items or indicating one-to-two word answers. Little space is allowed for free-text comments although they can be recorded in the system. Twenty-six questions are answered per patient and an additional twenty-five questions are answered for each birth.

This database is of interest for a number of reasons:

1) The collaborations among the Neonatology Database, Mineral-Homeostasis and Mineralization Database, and this database will yield medical benefits for all three. Approximately 23% of the admissions to the NICU recorded in the Neonatology Database will also have information in the Obstetrics Database because of the mother's admission to Barnes Hospital.

2) The same data represent two views, i.e., mother and infant, due to the possibility of multiple births. Users should be able easily to express queries which require counts of mothers or infants for the same data items.

3) This is the first database which was established with consistency checking included at its inception. Our experience so far has been that the compulsory checking of data items has complemented our efforts to encourage residents to be consistent. Potential problems have been identified and solutions defined early in the history of the database.

4) Finally, data are collected by house staff rather than special research nurses. This change gives us an opportunity to evaluate the difference in the kinds of errors made by the two groups.

Currently, there are 1435 patients recorded in the database. All potential problems identified by the consistency checks have been brought to the attention of the obstetrician in charge. Because of these findings, modifications have been made to both patient data and the tables where most consistency checks are maintained. The number of problems discovered by the system has been decreasing, as has the number of items left blank.

A special research database on mothers who suffer pre-term rupture of their membrane has also been defined. The data items to be stored

have been identified and there are 319 mothers registered in the system. Research data have been entered for a subset of these patients. These data are being gathered in a local clinical trial which is evaluating the advantages and problems associated with the use of tocolytics and/or glucocorticoids in patients with this serious complication.

## D-5. SCOR Patient Information Database

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Support: RR 00396
HL 17646

The Specialized Center of Research (SCOR) database (PR 16, D-4) currently contains information pertinent to 658 patients having suffered acute myocardial infarction and 280 patients followed to observe the incidence of early recurrent infarction (ERI). The variables contained therein describe the patients' cardiovascular history, in-hospital course, and long-term progress via follow-up examinations. Each patient is followed every three months for a year following the index episode, and then yearly thereafter. The data records are entered onto disk using the Interdata 7/16 computer system in the coronary care unit and then transferred via magnetic tape to the IBM System/360-370 at the University's Computing Facilities. There a permanent SAS database is maintained for analysis of the results of a variety of clinical studies.

The system's design and the limited number of patients and variables currently retained limit the questions that can be answered and make the process of analysis cumbersome. Preliminary plans were developed for a new database which would lead to improvements in the size of the patient population, the number of variables retained, and the method of operation. It was established that this new database could share software with the Neonatology Database (D-2). An initial information structure was designed, but because of support limitations there are no current plans for carrying the development further.

## E. Speech and Hearing

This year concludes a fruitful, ten-year formal collaboration with Central Institute for the Deaf. Researchers at CID plan to continue recent directions of research in speech and hearing using resources developed during this collaborative period. These resources include a Digital Methods Laboratory, a central processing facility, and a variety of satellite systems that serve as programmable laboratory controllers and sources of complex stimuli. The appreciation of this collaboration by the researchers at CID is supported by the heavy use these facilities are now receiving.

Early collaboration with Central Institute for the Deaf resulted in the development of digital instrumentation suited to speech-and-hearing research. The first systems that were developed, a Random-Access, Programmable (RAP-I) digital recorder, a computer system for processing sampled speech, and a RAP-II system that is interfaced to the LINC computer in the physiology laboratory, continue to be used in a variety of research applications, including the analysis of sampled speech sounds and glottal-source waveforms and the synthesis and tailoring of speech sounds for psychoacoustic experiments with human and animal subjects.

The proven usefulness of these first systems has led to the development of newer RAP systems that can be programmed to accommodate a variety of psychoacoustic experiments and a central computer system with increased data-sampling capability. This work is finished and the psychoacoustics, comparative psychoacoustics, and signal detection laboratories at Central Institute for the Deaf have been renovated to accommodate these new systems.

More recently, a major emphasis has been directed towards certain basic questions related to hearing and deafness that required the digital instrumentation available through the collaboration. These areas of study included the following: 1) measurements of psychophysical characteristics of electrocutaneous stimulation to determine if this sensory modality can serve as a substitute input for speech for profoundly deaf patients, 2) the measurement of glottal-source characteristics of normal and deaf talkers, 3) the development of methods for generating rapidly changing visual displays that can be used in lipreading studies, 4) psychoacoustic studies related to questions of speech perception and 5) the use of digital techniques for synthesis of calibrated complex tones for studying cochlear microphonics.

A major focus of the psychoacoustic studies is to understand those acoustic and neural transformations which are important to speech perception. Towards this goal, we have studied the spectral characteristics of natural vowel sounds with a psychophysically-based model of hearing and have undertaken a comprehensive study of proposed methods of vowel normalization to determine their relative merits. This work has continued this year in the study of vowel differences related to consonantal environment, rate of speaking, and sex of talker (E-5).

## E-1. Computer System for Auditory Research

Personnel: A. M. Engebretson, BCL and Central Institute for the Deaf
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J. P. Tadlock, Central Institute for the Deaf

Support: RR 00396
NS 03856

The RAP-IV system has been assembled and installed in the Signal Detection Laboratory at Central Institute for the Deaf. This system includes a NOVA 4-X computer with 256 kbytes of memory, multiply/divide hardware, a Model 8388 floating point unit and a set of RAP subsystems. The RAP subsystems include two Pertec 3400 series disk drives that can be used for program and data storage and that are compatible with other systems at CID and BCL, two 2-channel analog subsystems, a laboratory station driver subsystem, and an 8-channel signal-attenuator subsystem. This system adds significantly to the signal processing and laboratory control capability of the Signal Detection Laboratory.

The PC-1200 based speech and hearing system and the sound booth that presently reside in BCL will be moved to newly renovated areas in the clinics and research building at CID. This will complete the current phase of laboratory renovation.

## E-2. Speech Microscope

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J. L. Lauter, Ph.D., Central Institute for the Deaf
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Support: RR 00396
NS 03856

One method of estimating the formant frequencies, bandwidths and spectra of speech sounds is Linear Predictor (LP) analysis, which is incorporated into the Speech Microscope program (PR 16, E-2; PR 15, E-2). Because of the inherent assumption of LP analysis that the speech signal is the output of an all-pole filter modeling the vocal tract, nasals, nasalized vowels, plosives and fricatives cannot be adequately analyzed using LP analysis as they have zeros in their spectra in addition to poles. A pole-zero analysis program has been written in FORTRAN and made a part of the Speech Microscope program. This is an iterative procedure and consists of the following steps in each iteration. For

a specification of m poles and n zeros the steps are: (1) filtering of the speech signal by an inverse of the current estimate of the zero-filter to approximately cancel out the effect of the zero; let us call the output of the inverse zero-filter the theta signal, which essentially has an all-pole spectrum, (2) an (m+n)th order LP analysis of the theta signal and computation of the LP residue signal which is considered the input signal to the pole-zero filter, and (3) computation of more accurate values for the pole-zero filter coefficients using the current estimate of the input signal and the specified speech signal; this involves the inversion of a matrix whose elements are the auto- and cross-correlation coefficients of the speech and the input signals. The program displays the pole-zero spectrum and the locations of poles and zeros in z-plane at the end of each iteration. Preliminary analyses of nasals /m/ and /n/ indicate that for values of m around 23 and n around 26, the program converges in 5 to 6 iterations and gives a pole-zero spectrum closely matched to the speech spectrum.

## E-3. Accuracy of Formant Frequency Measurements

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NS 03856

The determination of formant frequencies has traditionally been an important aspect of the acoustic study of speech. The general theory of speech production is based upon the specification of formant frequencies and their physical relation to the vocal tract as a kind of resonating tube. While there is no generally accepted theory of speech perception, most current theories are based upon a determination of formant frequencies and some sort of further abstraction and normalization of those formant values. Furthermore, many useful studies of speech production have been made by measurement of vowel formant frequencies. However, despite the obvious basic importance of formant frequencies in speech research and in our theories about speech, the accuracy with which they can be determined has not previously been examined rigorously. When we desire to measure the formants of a given vowel, how accurately can we do so?

There are many different techniques for the measurement of formant frequencies, but there are only two which have been put into wide use. The traditional method is that of spectrography. This technique uses a wideband (300-Hz analyzing filter) spectrogram of speech and a narrowband (45-Hz analyzing filter) section in order to graphically, and with pencil and ruler, arrive at the center frequencies of the formants. Studies which have used this method include the following: Peterson and Barney,[1]

Angelocci, Kopp, and Holbrook,[2] Eguchi and Hirsh,[3] Monsen.[4] A quite different and newer technique for measuring formant frequencies is linear prediction analysis (Atal and Hanauer,[5] Wakita,[6] and Atal and Schroeder[7]). In comparison with spectrographic techniques, linear prediction analysis is quite different in that it does not depend upon a frequency analysis of the waveform. Instead, it uses a model of the vocal tract, and measures the extent to which samples of a given vowel waveform deviate from randomness in such a way that can be attributed to the characteristics of the system which produced the waveform, i.e., a vocal tract of a particular shape.

To evaluate the accuracy of formant frequency measurement techniques, speech samples were synthesized (by parallel synthesis) with known formant frequency values. The tokens were all 250-msec in duration, and in each token there were no changes of formant frequency, formant bandwidth, or fundamental frequency. The tokens were grouped into nine sets of ten. Within each set, the tokens differed only as to fundamental frequency, from 100 Hz to 400 Hz. This more than covers the $F_0$ range that might be encountered in natural speech, where 400 Hz is perhaps the upward limit of fundamental frequencies for juveniles. Each of the nine sets then conformed to a single bandwidth and formant frequency configuration, chosen from Peterson and Barney average values to represent some of the typical and extreme conditions found among vowels, e.g. /i/, /u/, /æ/, /r/, and /ɔ/. The vowel /æ/ was also used in four different sets which differed as to bandwidths, from 50 Hz to 400 Hz.

These tokens were measured spectrographically by three different experienced readers: Ilse Lehiste, Robert Port, and Victor Zue. The tokens were also analyzed by linear prediction, using the CID Speech Microscope. The measured values obtained by both techniques were then compared with the actual values. The amount of error involved in the estimation of $F_1$ and $F_2$ is nearly the same for both linear prediction analysis and for human spectrographic analysis. For all nine sets of tokens, the mean error is $\pm$ 69 Hz via linear prediction and $\pm$ 73 Hz via spectrographic means for $F_1$, and the error is $\pm$ 57 Hz (linear prediction) and $\pm$ 42 Hz (spectrographic means) for $F_2$. For the estimation of $F_3$, however, analysis by linear prediction is superior: an average error of $\pm$ 50 Hz was obtained via linear prediction, whereas the error via spectrographic means was $\pm$ 121 Hz. The averages just quoted are for frequencies between 100 and 350 Hz, although the same tendencies are apparent in the data for the frequencies between 100 and 500 Hz.

When formant frequencies are estimated by linear prediction, the error is approximately the same for all fundamental frequencies between 100 and 350 Hz. Above 350 Hz, a sudden increase (about 300%) in the rate of error occurs. In contrast to this, when formants are estimated by spectrograms, there is a gradual increase in the rate of error as fundamental frequency increases; it is quite noticeable even at 200 Hz. For spectrographic techniques, the accuracy of measurement is a function of the fundamental frequency. An increase in formant

bandwidth or the close proximity of two formants reduces the accuracy of measurement for both methods.

A clear implication of this study is that if formant frequencies are to be measured in a subject population in which there are considerable differences of fundamental frequency (for example, men, women, and children), then linear prediction should be the measurement technique to be used.


1. G. E. Peterson and H. L. Barney, "Control Methods Used in a Study of the Vowels," Journal of the Acoustical Society of America, vol. 24, pp. 175-184, 1952.

2. A. Angelocci, G. Kopp, and A. Holbrook, "The Vowel Formants of Deaf and Normal-hearing Eleven- to Fourteen-year-old Boys," Journal of Speech and Hearing Disorders, vol. 29, pp. 156-170, 1964.

3. S. Eguchi and I. J. Hirsh, "Development of Speech Sounds in Children," Acta Otolaryngolica, supplement 257, 1969.

4. R. B. Monsen, "Normal and Reduced Phonological Space: The Production of English Vowels by Deaf Adolescents," Journal of Phonetics, vol. 4, pp. 189-198, 1976.

5. B. S. Atal and S. L. Hanauer, "Speech Analysis and Synthesis by Linear Prediction of the Speech Wave," Journal of the Acoustical Society of America, vol. 50, pp. 637-644, 1971.

6. H. Wakita, "Direct Estimation of the Vocal Tract Shape by Inverse Filtering of the Acoustic Speech Waveform," IEEE Transactions on Audio and Electroacoustics, vol. AV-21, no. 5, pp. 417-427, 1973.

7. B. S. Atal and M. R. Schroeder, "Linear Prediction Analysis of Speech based on a Pole-zero Representation," Journal of the Acoustical Society of America, vol. 64, pp. 1310-1318, 1978.

## E-4. Synthesis of Consonant-Vowel Syllables with Female Attributes

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Support: RR 00396
NS 03856

Six continuant consonant-vowel syllables (vis. /la, ra, ma, na, wa, ja/) were synthesized using Klatt's model[1] in conjunction with readily available CID subroutines. The program for synthesis was implemented on the Speech and Hearing computer system and allows fundamental frequency, formants and bandwidths to change as a function of time. Values of formant frequencies and bandwidths were obtained from Klatt (personal communication). Values for fundamental frequency and timing of formant transitions were obtained from our previous analysis of five female talkers with the speech microscope (PR 16, E-5). To synthesize intelligible natural-sounding tokens, it appeared necessary that formant bandwidths vary independently of formant values. The nasal sounds, /ma/ and /na/, required a balance of nasal poles and zeros to approximate natural speech. To date, acceptable tokens of all six syllables have been synthesized with various durations (330, 350, and 400 msec) and various intonation contours. The variations of fundamental frequency in a series of three-syllable stimuli range from an adult intonation pattern which varies from 180 to 220 Hz, to an infant-directed pattern (motherese), which varies from 180 to 350 Hz. These syllables are presently being used as stimuli for experiments on speech-perception abilities of infants.

1. D. H. Klatt, "Software for a Cascade/Parallel Formant Synthesizer," Journal of the Acoustical Society of America, vol. 67, pp. 971-995, 1980.

E-5. Vowel Normalization: Differences Related to Consonantal Environment, Rate of Speaking, and Sex of Talker

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NS 03856

Last year, Miller, Engebretson, and Vemula[1] reported that the relevant acoustic characteristics of steady-state vowels would be well characterized by the vector {log (F1/F0), log (F2/F1), log (F3/F2)} where F1, F2, and F3 are estimates of the center frequencies of the first three resonances (formants) of the vocal tract and where F0 is the fundamental frequency for women and children and about 1.43 times the fundamental for men. This generalization is based on the mean values of F0, F1, F2, and F3 for each of ten vowels published by Peterson and Barney.[2] When this same vector was applied to the data for the individual talkers of Peterson and Barney, the vowels were only poorly separated in the space. It was argued that this happened because the values of F0, F1, F2, and F3 change over-time and that auditory system must extract an average in order to characterize a vowel in a naturally spoken syllable.

Therefore, we chose to record three vowels (Vs) that are known to be highly influenced by the consonant surround.[3] The three vowels, /I/ (as in bid), /ɛ/ (as in bed), and /ʌ/ (as in bud), were spoken by four talkers, two male and two female, in the contexts /bVb/, /bVd/, /dVb/, and /dVd/. The talkers were instructed to speak the syllables one time at a normal rate and another time as rapidly as possible without mispronunciation. Finally, the talkers were asked to sustain each vowel in a prolonged /bVb/ syllable so that the characteristics of the sustained vowel could be measured. Broadband spectrograms were made of each syllable. In addition, the following measurements have been made with the speech microscope. The beginning and the ends of the vocalic portions of the syllable were located and the duration (T) noted. Then spectral analyses were conducted at times 0T, .25T, .50T, .75T, and 1.0T. A Kaiser-Bessel window was adjusted to include exactly two pitch periods at each sample point. A 24-pole linear-predictor (LP) analysis was calculated and this compared to a discrete Fourier transform (DFT) calculated on the same windowed waveform. The fundamental frequency (F0) and the center frequencies and bandwidths of the first three formants were then taken from the LP-analysis with the following exception. When two "formants" were reasonable candidates for a "single" formant, as could be inferred from the values themselves, the DFT, or the patterns of nearby spectra, then center frequencies of the candidate formants were averaged but weighted by their relative Qs. Thus, the candidate with narrower bandwidth was given more weight. The resulting "tracks" for F0, F1, F2, and F3 are now being studied to determine reasonable metrics that produce the

best "clustering" of the vowels independently of talker, talking rate, and consonant surround.

Our hypothesis was that an average of the vectors {log (F1/F0), log (F2/F1), log (F3/F2)} at the times across the middle of the syllable, for example, the average vector for .25T, .5T, and .75T, would characterize the vowels better than the vector for any single time. This appears not to be the case. Rather, the vowels appear to reach a "target" value of the vector at a time that falls between 25% and 50% of the way through the vocalic portion of the syllable. Therefore, a detailed study of the vowel spectra at 0.3125T, 0.3705T, and 0.4375T is being made.

As before, it is emphasized that we think that it is the spectral shape in log dimensions that characterize the vowel and that vector {log (F1/F0), log (F2/F1), log (F3/F2)} characterizes a vowel only to the degree that it reflects the corresponding spectral shape.


1. J. D. Miller, A. M. Engebretson and N. R. Vemula, "Vowel Normalization: Differences Between Vowels Spoken by Children, Women, and Men," Journal of the Acoustical Society of America, vol. 68, supplement 1, p. 533, 1980 (abstract). (See also, BCL PR 16, pp. 140-142; June, 1980.)

2. G. E. Peterson and H. L. Barney, "Control Methods Used in the Study of the Vowels," Journal of the Acoustical Society of America, vol. 24, pp. 175-184, 1952.

3. K. N. Stevens and A. S. House, "Journal of Speech and Hearing Research, vol. 6, pp. 111-128, 1963.

## F. Supporting Activities

Activities at BCL which contribute to the goals of more than one major program of the laboratory or address the needs of individual users who can benefit from the special expertise of the staff and the inventory of computer and test equipment are called supporting activities. Service to users does not follow the usual computation-center pattern. No fee schedule has been established, nor is there a centralized facility. Instead, senior laboratory staff members consider requests from investigators for assistance in addressing biomedical computing problems. Investigators may be directed to commercial vendors or existing fee-for-service facilities. Other researchers may be advised of the unavailability of appropriate technology. The remaining investigators may have problems that match the special capabilities within BCL. Usually, such a project is assigned to a staff member with similar experience. If the project can be completed quickly, the investigator has his or her results and a short note describing the work will appear in the annual report and in the open literature if appropriate. Other projects occasionally prove impractical and the best alternative is recommended. A few of the user projects may develop into major initiatives within the laboratory. Most of the major projects began in this fashion and we value the opportunities that supporting activities provide.

Although the projects reported in this section span a variety of topics, they can be grouped conveniently as biomedical applications, system development aids, and digital hardware designs. The biomedical applications represent new initiatives in which basic explorations are being conducted, which may or may not ultimately result in a major, long term program. One example is the continued collaboration with the Department of Biochemistry relating to the development of microcomputer systems for laboratory automation. The previously reported DNA restriction-mapping studies have matured to the extent that they are now reported under Systems for Specialized Biomedical Studies (C-2). Even in cases where an extended effort does not materialize, the relationships which are cultivated frequently prove beneficial to future work.

System development aids mostly benefit the BCL staff, but also are utilized by other groups where appropriate. An excellent example here is the microprocessor development support which, although still evolving, is an almost routine tool used in data acquisition, signal processing, and control applications. System software developments reported here are also widely used in supporting a variety of projects.

The digital hardware designs reported in this section are frequently one-time, special-purpose designs. The design of the interface for the Biomation 8100 waveform recorder is an example of such a project. In contrast, other designs may have wide appeal and construction of multiple copies is envisioned. The experimental local-area network is such a design.

F-1. Microprocessor Development Support

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R. E. Hitchens, BCL
T. J. Holmes, BCL
G. C. Johns, B.S., Computer Systems Laboratory
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Support: RR 00396
HL 25944
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Software and hardware development for 8-bit microprocessors continues to be supported by FORTRAN-based cross-assemblers (FOCRAS) and intelligent consoles (Inc) as reported previously (PR 16, G-1). These software and hardware development tools are available for the M6800, the M6802 and the I8080 microprocessors.

Our microprocessor support facilities have been expanded to include software and hardware development support for the Motorola M68000 16-bit microprocessor. Our approach, as characterized in Figure 1, is to capitalize on the availability of host computers for software development and a test environment supported by debugging monitors, logic analyzers, and in-circuit emulation capabilities. Motorola's FORTRAN based cross-assembler for the M68000 has been installed on PDP-11/34s under RT-11 and RSX-11M, on TI-980s under MIST-980 and on an IBM/370 with access through the MUSIC interactive system. A C-to-M68000 cross compiler obtained from the MIT Real Time Programming Group is being installed on a PDP-11/34 under UNIX. A General Radio model 2301 development system which provides a serial link to host computers and in-circuit emulation for the M68000 has been purchased and installed.

An Advanced Micro Computers System 29 has been purchased to facilitate the development of hardware and micro-control software for special purpose processors based on the AMD 2900 series of components. It is currently in use in the development of a micro-coded machine to be used as a portion of the PETT Time-of-Flight Data Acquisition System (B-14).

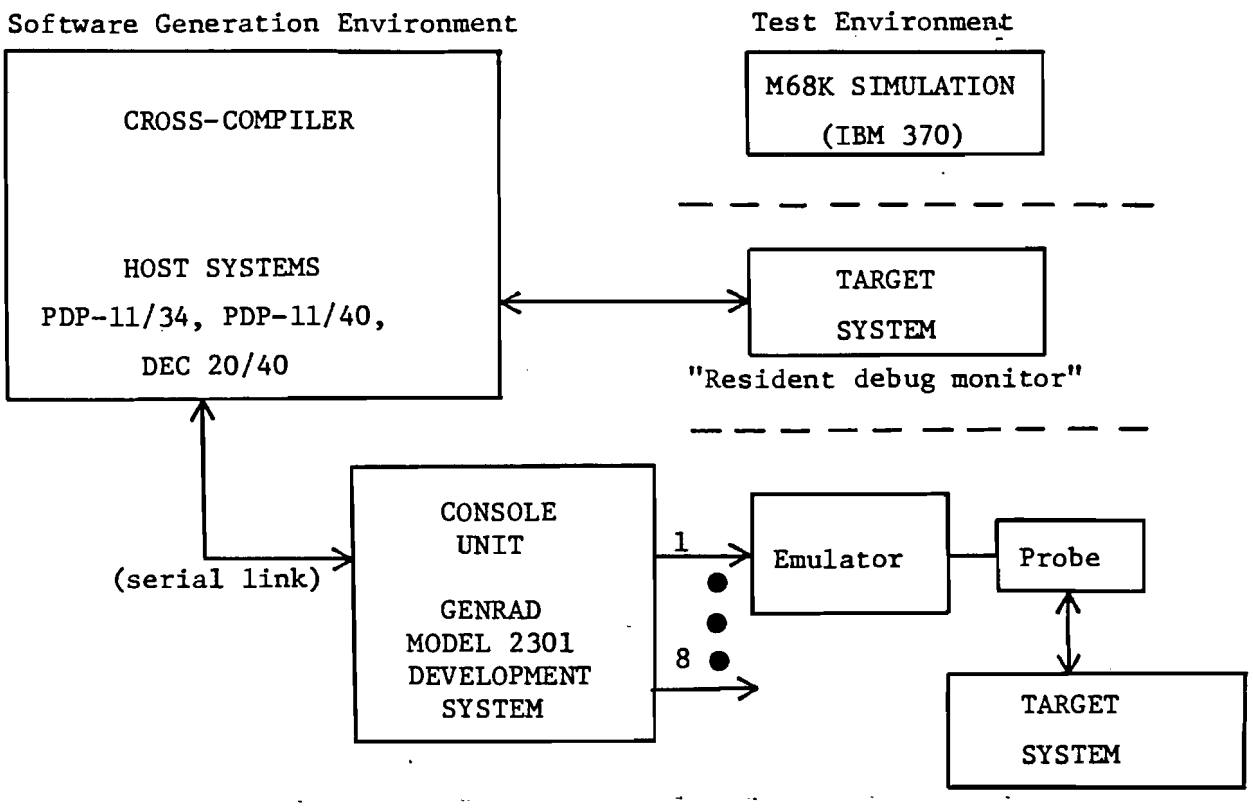


Figure 1

Cross-software generation coupled with a multifaceted test environment including a simulation facility, a ROM based debug monitor, and in-circuit emulation provides a complete development environment.

## F-2. PDP-11/34 Configurations for Engineering Hardware and Software Support

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S. R. Phillips, BCL

Support: RR 00396

Two PDP-11/34 systems have been assembled to support activities at BCL: one devoted to real-time, graphics and image processing tasks under RT-11 and another devoted to entry and editing of computer programs, general text editing, and other computing tasks not requiring special hardware under RSX-11M (F-3).

The first system contains 124K words of memory, a floating-point processor, a serial interface for communication with other systems and a line printer. Mass storage includes 10 Mbyte of RK-05 equivalent disks and a dual-floppy-disk system. Graphics peripherals include a Lexidata System 3400 color raster display with writeable control store and a Versatec 200 point-per-inch printer/plotter. A 16-bit parallel digital port is available for interfacing special apparatus. Future plans call for the addition of 80 Mbyte of additional disk storage.

The second system contains 124K words of memory, a floating-point processor, a 1K word cache memory to improve system response under heavy loading, nine serial interfaces for terminals and communication lines and a line printer. Mass storage consists of two 80-Mbyte disks, an 800/1600 bit-per-inch tape system and 5 Mbyte of RK-05 equivalent disks. A direct memory access interface to the Versatec printer/plotter reduces system overhead considerably when operating in the plot mode.

## F-3. Introduction of RSX-11M for Software Support

Personnel: R. E. Hermes, BCL
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D. W. Stein, Jr., BCL

Support: RR 00396

A review of usage patterns of current computing resources at BCL has led to the local introduction of the RSX-11M System, a product of the Digital Equipment Corporation. We have chosen to implement the RSX-11M System on the PDP-11/34 configuration described in F-2.

The RSX-11M system is a disk-based real-time operating system which provides maximum utilization of system resources. The system allows program

development and real-time tasks to operate concurrently through the use of assigned task priorities, a round-robin scheduler, and executive-level disc swapping. The system permits programs in memory to be as large as 32K words. A large variety of utilities are available, in addition to several text editors.

Software available with the system includes an extended and optimized FORTRAN compiler (FORTRAN IV Plus), an assembler (MACRO 11), and two text editors. In addition, we have added a full-screen text editor (EMACS), a FORTRAN preprocessor language (RATFOR), and a text formatter (RUNOFF). Other software also is available through DECUS, a DEC systems user group.

The system currently has twenty active users who share four CRT terminals and one dial-up modem for remote access to the system. Use of the system has been dominated by text editing, but has also included the execution of computationally demanding FORTRAN programs which have required several days of run time. Since the system has media compatability with other in-house systems, programs are often developed on RSX-11M and then transferred to other systems. As a result of the introduction of this system, we have been able to better utilize other computer systems as a result of more flexibility in task allocations. Further acquisition and development of new systems software will enhance the system's usefulness in the future.

## F-4. Software Support for Image Processing and Display

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S. R. Prothero, BCL
D. W. Stein, Jr., BCL

Support: RR 00396

The use of several Lexidata 3400 raster-scan image and graphics processors in a number of research projects (C-1, C-2, D-1) has necessitated considerable software development efforts to facilitate the use of these devices. Efforts have been divided along several lines: general-purpose image-manipulation and display software, software support for VLSI design, DNA-mapping data-display software, and a relocatable macro cross-assembler and linker.

During the summer of 1980 a wide variety of RATFOR programs were written to permit convenient storage, manipulation, and display of images, interactive setup and verification of the display system's color look-up tables, and loading of microprograms into the Lexidata's writable control store (WCS). An RT-11 driver for use on Q-BUS-based LSI 11 systems also was written and debugged.

An interactive system for viewing VLSI circuits was written during the spring of 1981. Previous work allowed display files to be captured from the university's DEC-20 and displayed on the Lexidata. The viewing system gives the user the ability to interactively examine circuit features via zoom, scroll and color highlighting, controlled locally by a PDP 11/40, with better response time than is possible with a similar view station controlled by the DEC-20. Other system features of interest allow the user to draw figures on the Lexidata, to reposition and duplicate areas, and to store figures on secondary storage for later recall.

Software for display and processing of data obtained from linear scans of electrophoretic gels has been developed. The linear-array imager used does not, by itself, generate a picture to aid in aiming and focusing. Use of software which produces a two-dimensional display on the Lexidata of the camera image has proven very helpful.

Early microcoded programs were cross-assembled using a less than satisfactory cross-assembler supplied by the equipment manufacturer. As a result, the utility of the WCS feature was severely restricted. As several new microcoding efforts were contemplated, it was felt that an improved microcode development environment was needed. Accordingly, a relocatable, conditional macro assembler for the Lexidata 3400 (LAP/34), and LEXLNK, its assompanying linking loader were created. Both LAP/34 and LEXLNK are written in RATFOR, a structured dialect of FORTRAN, and run under RT-11 or RSX-11M. Modifications to permit these programs to run on any machine whose FORTRAN language processor supports byte-formatted data types and direct-access files are relatively simple.

Design, coding, and debugging of both programs has been completed, and several test microprograms have been written, assembled, linked, and run. A user guide has been written (Monograph No. 400) and a programmer's reference is in preparation.

## F-5. Evaluation of Winchester Disks and Controllers

Personnel: R. E. Hitchens, BCL
R. W. Hagen, BCL

Support: RR 00396

Several BCL research activities may benefit from the decreased data storage costs and the increased performance of Winchester technology disk drives. These potential benefits have motivated an evaluation of commercially available Winchester drives and compatible controllers. After comparing the published specifications, costs and availability of drives and controllers from several manufacturers, two different models of each component were acquired for testing.

A Microcomputer Systems Corporation model MSC-9305 controller has been coupled with a Seagate Technology model ST-506 drive. This configuration provides a 5-Mbyte formatted storage capacity which is compatible with the IEEE-488 interface bus. The initial tests demonstrated a convenient protocol for communicating between the host system and the disk controller. Plans are to increase the data storage capacity of a data-acquisition system (C-6) by incorporating an ST-506 micro Winchester drive and an MSC-9305 controller into the existing IEEE-488 compatible system.

A Shugart model SA1404 controller has been coupled with a Shugart model SA4008 14-inch 28 Mbyte drive. This controller has a general purpose interface and is therefore applicable to many different processors through the design of an appropriate bus interface. The system has been interfaced to the parallel input/output port of an M68000 Versamodule system for initial testing and evaluation.

## F-6. An IEEE-488 Bus Interface for the Biomation 8100 Waveform Recorder

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R. W. Hagen, BCL
D. W. Stein, Jr., BCL

Support: RR 00396
Washington University

The Biomation 8100 can be described functionally as a fast, programmable, digital oscilloscope with memory. A previous report elaborates on the application of the Biomation unit (PR 15, B-1). This interface was developed to meet the following objectives:

1. to accept an input mnemonic command string sent over an IEEE-488 instrument bus,

2. to interpret the input commands,

3. to send the interpreted instructions to the Biomation 8100, and

4. to transmit Biomation output over an IEEE-488 bus.

A host-independent interface controller was implemented, using a Motorola MC6802 microprocessor, to communicate over an IEEE-488 bus. A mnemonic representation of the Biomation's command language was defined to simplify remote characterization of the settings of the Biomation's functions. The interface conducts all the handshaking with the Biomation necessary to implement the commands and to receive the Biomation's 2048 x 8-bit sample memory.

The interface system simplifies the acquisition of a digitized waveform from the Biomation by the introduction of a mnemonic command language thereby insulating the user from the Biomation's singular and confusing protocol.

## F-7. Optical Communication Experiment

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ENG 76-11565
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The Washington University School of Engineering and Applied Science (SEAS) is located on the central campus, which is about 3.5 km from the Medical School campus where the BCL is located. Motivated both by an increasing need for data communication between the BCL and the SEAS and the increasing cost of telephone service, we initiated an experiment to determine the feasibility of implementing a high-data-rate (> 1 Mbit/sec) communication link between the BCL and the SEAS utilizing a solid-state infrared laser as a carrier. The goal of the experiment is to measure properties of the optical path that are important in the design of such a communication system. It is expected that clear-air atmospheric turbulence will introduce severe fading because of the long path length, so this is an issue receiving particular attention.

## F-8. An Experimental Local Area Network

Personnel: G. J. Blaine, BCL
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A. J. Gray, BCL
S. R. Phillips, BCL
C. D. Shum, BCL

Support: RR 00396
Washington University

Increasing service charges for leased lines and a desire to access multiple host computer resources (including PDP-11/RSX-11M, DEC20/TOPS20,

IBM 370/MUSIC, PDP-11/UNIX, TANDEM/MUMPS) from distributed data terminal locations motivates the development of a communication environment supported by a local area network. Currently, cost and availability have deterred the acquisition and deployment of such a network within the Washington University research community. The experience gained through our summer workshop project known as "Schoolbus" accented the heavy investment required for development of a local area network with an embedded operating system of sufficient utility to address the requirements for communications between heterogeneous computing systems.

A modest pilot experiment has been defined to establish insights helpful to a second generation procurement or development. Our goal is to address terminal-to-host computer interconnection which allows physical dispersement of both terminals and resources within our building complex while requiring no modifications to the various host operating systems, thus avoiding investment in a network operating system and keeping the system design simple and describable. Our interconnect network is to appear as a "transparent element" inserted at the physical protocol layer as in the dial-telephone/acoustic coupler paradigm.

Principal features include: fixed assignment of time slots for transmission (to eliminate contention for the interconnect resource), assignment of resources on a first-come/first-served basis (as in a dial-up network), error control via existing host-terminal protocol for error detection and correction and single data character packets. Our target implementation utilizes TV-field and line-synchronization standards for generation of fixed time slots, and provides 30 channels at up to 4800 bits per second. Coaxial cable will provide a multi-access bidirectional communications medium for distribution over distances of less than 1000 feet. Channel access is provided by a M6802 microprocessor-based tap unit with transmitter and receiver capability. The tap unit has been designed and two are being constructed for initial testing and evaluation.

1. G. J. Blaine, "A Proposal for a Modest Local Area Network Experiment," Working Note No. 10, Biomedical Computer Laboratory, February 1981.

F-9. Software Modules for Instrument Control

Personnel: W. F. Holmes, BCL
M. C. Jost, BCL

Support: RR 00396

The continued development of a system of programs destined for long-term use requires changes in hardware from time to time as the present equipment becomes unmaintainable, obsolete, or outmoded. Conversion of software to a new computer is greatly simplified by writing the software in a standard higher level language. However, computer systems used for instrument control have specialized hardware and requirements for real-time processing not handled by standard languages. We are dealing with this problem now, as we convert our mass spectrometry computer system from a Computer Automation LSI-2 computer to a Digital Equipment PDP-11/23. The LSI-2 computer is the central processor in a set of hardware modules that we have designed over the years. In particular, there is a high speed, refreshable, graphic display with a built-in vector generator, that would be extremely costly to replace. We have examined several quite different graphic display devices that could serve as potential replacements for the graphic display hardware: the VT-55 terminal, and two random-access video graphics interfaces. All have drawbacks compared with the present hardware, such as speed and versatility. Thus we have chosen to make the conversion in stages in order to preserve the specialized I/O hardware, until suitable replacements become available at affordable design or purchase costs.

The PDP-11/23 becomes the new central processor, replacing the LSI-2. All data processing occurs on this computer. The LSI-2 is not discarded, however, and it becomes a programmable I/O controller. Its programs are kept very simple by using data tables generated by the PDP-11/23, which are interpreted in the LSI-2. For display, these tables contain codes and coordinates representing points, lines, and characters, which are easily generated by programs written in a higher-level language. Thus, the data table concept will allow a smooth transition from old to new hardware.

The LSI-2 software is nearly complete. We have written a communication handler, and almost finished a display interpreter. We will also use the table concept for data acquisition, generating a table of digital-to-analog converter settings with the times for each setting, and a buffer for analog-to-digital converter values. Implementation of table-driven data acquisition will require a clock, the converters, and a very simple interpreter. The interpreter may be written for either processor, depending on our progress in developing new interfaces.

F-10. Compliance with Topical Ophthalmic Therapy

Personnel: D. W. Meltzer, M.D., Ophthalmology
D. E. Beecher, BCL

Support: RR 00396
EY 03579

We have developed and are now using, an electronic device which is hidden within a bottle of eyedrops. The bottle and the device are dispensed to patients and the device records electronically each time the patient attempts to use his medication. Such studies are being performed in order to investigate the role of non-compliance with suggested medical therapy in treatment failure of ophthalmic disease. A large number of patients will be examined in the next several years using this technique. These experiments will investigate several issues including: (1) the percentage of patients who do not comply satisfactorily with suggested medical therapy; (2) the effect of patient education and patient-physician interaction on improving compliance; (3) the amount of deviation in compliance that can be tolerated in diseases such as glaucoma.

Each time a patient returns to the clinic, some 4,000 bits of information must be collected from the electronic device in the bottle. These data, which correspond to the usage times of the medication, then need to be processed and subjected to statistical analyses. In order to accomplish this, an interface unit has been built for an already existing PDP-11 computer within the Department of Ophthalmology. Software has been developed to allow the computer to read all 4,000 bits of data that are contained within the device and to store these on magnetic tape in a format suitable for later statistical analyses.

Software for handling the data is being implemented. The following modules have been written:

1. Acquisition of Device Data.
   This module acquires data from a memory chip which is incorporated in the dropper bottle.

2. Acquisition of Patient Information.
   This module prompts the computer operator for various patient information which includes:
   a) Identification Fields (6)
   b) Patient Name
   c) Bottle Start Time
   d) Patient Start Time
   e) Patient Return Time
   f) Time Interval of Bottle Readings
   g) Weight of Dispensed Bottle
   h) Weight of Returned Bottle

   All of the above information along with the actual bottle data is formatted and output to the line printer for immediate hardcopy.

3. Information Storage
   A master tape containing all patient records is retained on-site.

4. Generation of IBM-compatible Tapes
   Patient data are written onto tapes that are compatible with the IBM standard unlabeled tape format. The records are then transferred to an SAS database on the University's IBM 370.

Following integration and testing of the hardware and software, the system will be ready for routine use.

## F-11. PC-1200 Software Support

Personnel: D. W. Stein, Jr., BCL

Support: RR 00396

As usage of the PC-1200 systems declines, so does the amount of software support (PR 16, G-2). During the past year, effort was spent on software modification and development only at the request of a user.

UD, a new command, has been added to the existing BDOS operating system. This command allows the user to read a specified area or areas of a universal storage device (USD) floppy disk (PR 16, G-3) and store the data in a BDOS file.

Three subroutines received attention:

1) GPUSD, the general purpose USD read/write subroutine was modified to correct some errors.

2) A subroutine to do a bubble sort on a real array and return the sorted array indices as well as the sorted array was created from SORT.

3) A subroutine to read and write the calibration constants for RHO-THETA digitizer was written in order to facilitate the use of the RHO-THETA programs.

All programs are accompanied by appropriate documentation files.

Continuing a policy started last year, the new and updated software is contained on a separate tape, so that only users desiring the new programs need modify their existing BDOS systems.

F-12. Development of an Automated System for the Monitoring of Epileptic Patients with Epidural Electrode Arrays

Personnel: S. Goldring, M.D., Neurological Surgery
S. A. Golden, B.S., Neurological Surgery
P. Lombardo, B.A., Neurological Surgery

Support: NS 14834
Washington University

As indicated last year the crosspoint matrix (PR 15, F-2) has been expanded to allow monitoring of arrays with 52 electrodes. The full matrix now has been used with twenty patients and has performed well. Additional self-test software was added to the crosspoint matrix to detect discrepancies between the video display and the actual recording site. Grounding the matrix outputs as they enter the low-level EEG amplifiers was found to adequately quiet the pen writers during electrical stimulation of the brain. A prototype of the previously proposed EEG amplifier (PR 15, F-2) has been satisfactorily tested, and a bank of such amplifiers has been constructed and tested.

Software for control of our low-level EEG amplifiers has been implemented and the 16-channel A/D converter has been tested. Interfaces now are being constructed to allow serial transmission of the digitized data to the remote MINC computer for manipulation and from the computer back to local TV monitors to display the data. The video displays are generated by Matrox Electronics Systems alphanumeric and graphics boards, which are controlled by a M6800 processor board of our own design. An initial assembly language program for the MINC has been written to perform data averaging. It will be tested when the interface hardware has been constructed.

Plans are to develop the communication system to permit the transmission of sensory-evoked response (SER) signals from the operating room and various patient areas to the remotely located MINC. The communication system will have sufficient capacity to permit simultaneous monitoring of seizure activity and for collection of the SER. The monitoring system will be based on a PDP 11/34 (DEC) and will permit retention and display of sixteen channels of EEG from up to five seizure episodes.

F-13. Software Support for Perkin Elmer OS/32 Operating System

Personnel: D. E. Beecher, BCL

Support: RR 00396

In August of 1980, the department of Radiation Sciences had only one computer, a Perkin Elmer 7/32. The operating system revision level (version 3.2) was approximately 2 years out of date. To provide a more

suitable operating environment for that department and enhance the capabilities of that machine, the current version of OS/32 (version 5.1) was installed. The jump through two full version levels necessitated many changes in already existing software. Also, a substantial amount of new system-level software was developed to address the expanding needs of Radiation Sciences.

The installation of OS/32 version 5.1 also made it possible to support multiple users on the 7/32. This introduced further complications to the users. Since commands from the user terminals were slightly different than those from the operator's console, some re-education was needed to bring users up to date with the new and more powerful user interface.

In January of 1981 the Division of Radiation Sciences purchased a Perkin Elmer 3242 computer system with OS/32 version 5.2 to carry the bulk of their computing load. A much simpler re-education process then took place to familiarize users with both the new machine and the new operating sytem release.

A substantial amount of effort has also been expended in interfacing various peripherals to the Perkin Elmer 3242. The following peripherals have been added to the system:

1. Ramtek 9400 Graphic Display System
2. Versatec Printer
3. PETT VI Scanner Interface
4. Matrix Camera (for hardcopy film-type images)
5. Various Color and Black-and-White Display Monitors

The following peripheral interfaces are also being considered:

1. Graphics Tablet
2. Versatec Plotter
3. Floppy Disc Subsystem
4. Array Processors

Documentation is being revised to reflect continuing changes in the computing environment in Radiation Sciences.

## VI. INDUSTRIAL COLLABORATION

One of the goals of the Biomedical Computer Laboratory is to foster the commercial development of useful medical computer systems. Industrial collaboration provides an additional outlet for laboratory developments and benefits the staff by keeping it abreast of the practical considerations of reliability, maintainability, and cost. Progress being made in this important phase of the laboratory's activities is summarized here.

A. Arrhythmia Monitoring. Longstanding collaboration (PR 15, VI-A) with the Mennen-Medical Company (formerly Mennen-Greatbatch) continues in the areas of algorithm and experience sharing of the new QRS detector/delineator (A-1). Concepts originally tested at BCL in a Holter-tape processing environment have been applied to Mennen's monitoring system where they are now undergoing evaluation in the real-time environment. (BCL personnel: K. W. Clark, C. N. Mead, L. J. Thomas, Jr.)

B. Collaborative Drug Studies. The Argus/2H computer system[1] was used to analyze long-term ECG recordings in conjunction with a drug study of LB-46, a beta-adrenergic antagonist under development by Sandoz-Wander, Inc. (PR 16, VI). Argus/2H is now being used for two other drug studies sponsored by American Critical Care and Mead Johnson.

American Critical Care. A "Comparison of the Efficacies of Bretylol and Procainamide in the Treatment of Ventricular Arrhythmias Resistant to Lidocaine" has been underway at Barnes Hospital and several other medical centers across the country. The one-year study is a randomized, open parallel comparison of two active drugs, procainamide and bretylol. The primary efficacy variable has been the occurrence of ventricular tachycardia (VT) or ventricular fibrillation (VF) while on the study drug. Patients who have refractory ventricular premature beats (VPB's) are also entered into the study on the assumption that they are at risk of VT or VF. VPB frequency while on the study drug will be examined for trends, but the study is not designed to give definitive data on the effects of the study drugs on VPB frequency. Patients with VT or VF refractory to lidocaine have been grouped separately from those with VPB's refractory to lidocaine. These two groups have been in turn divided into patients with and patients without congestive heart failure (CHF). Within each of these four groups, assignment of patients to treatment with either bretylol injection or procainamide hydrochloride injection have been in accordance with a predetermined randomization schedule. As a result, there have been two treatment groups of approximately equal sizes within each of the four patient groups. Separate randomization schedules for the four groups have been prepared for each center by the Biometrics Department of American Critical Care. Stratification for CHF and non-CHF patients ensures comparability of patients in the two drug groups. The CHF and non-CHF groups will be combined in analysis. Target recruitment was 8-15 patients from each of 8 centers. At this time, termination of centers without sufficient patient entry has occurred. Washington University and Harborview Medical Center will remain as study participants while

patient entry continues. Three long-term (24-hour) electrocardiographic recordings (LTERs) will be obtained prior to, during, and after drug therapy. Although the physicians at each center may scan his/her own tapes, all tapes will be sent to BCL for analysis on the Argus/2H arrhythmia detection system.[1] Printed summaries are mailed to the investigator at each center and to American Critical Care.

Mead-Johnson. A study of encainide hydrochloride (Encainide) is underway at the Jewish Hospital of St. Louis and at several other medical centers across the country. An antiarrhythmic compound, Encainide is a benzanillide derivative with high potency although it is generally well-tolerated. It is free of anticholinergic effects and shows no negative inotropism in the presence of a normal cardiac index. In clinical studies, Encainide suppressed ventricular arrhythmias following either single or divided doses ranging from 25 to 150 mg.

The study consists of three protocols: (1) "Inpatient dose titration with Encainide in the treatment of non-life-threatening premature ventricular beats"; (2) "Outpatient dose titration with Encainide in the treatment of non-life-threatening premature ventricular beats"; and (3) "Continuing encainide therapy for patients with cardiac arrhythmias." The objectives of the first two protocols are to (a) evaluate the therapeutic ratio in a patient population devoid of life-threatening cardiac disease and (b) obtain oral dose titration efficacy data. The objectives of the third protocol are (a) to allow continuation of treatment for patients benefitting from previous encainide therapy and (b) to assess long-term arrhythmia control, the nature and severity of any adverse effects, and the continuing need for chronic treatment in these patients. Study design for the first two protocols is single-blind, placebo-controlled evaluation utilizing a q.i.d. dosage titrated according to a standard dosage regimen. The third study is an open evaluation of Encainide using dosages set for each patient by the patient's physician. To date 10 patients have begun one or more protocols.

In order to assess the efficacy of Encainide on arrhythmias, multiple long-term (24-hour) ECG recordings (LTERs) obtained during each protocol are analyzed by the Argus/2H arrhythmia analysis system.[1] Printed summaries of analyses are sent to Mead-Johnson via Jewish Hospital. Beat-by-beat data, in machine-readable form, are condensed into a SAS dataset,[2] which in turn is sent to Mead-Johnson.


1. K. W. Clark, R. E. Hitchens, J. A. Ritter, S. L. Rankin, C. N. Mead, S. M. Moore, S. J. Potter, G. C. Oliver, and L. J. Thomas, Jr., "A Computer System for the Processing of Dual-Channel Holter-Recorded Electrocardiograms," Proceedings of the BIOSIGMA '78 International Colloquium on Signals and Images in Medicine and Biology, Paris, France, pp. 79-86, April 1978.

2. J. P. Miller, J. A. Ritter, K. W., Clark, L. J. Thomas, Jr., and G. C. Oliver, "Extended Analysis of Argus/H Quantified Ventricular Ectopic Activity," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 76CH1160-1C, St. Louis, Missouri, pp. 165-170, October 7-9, 1976.

## VII. TRAINING ACTIVITIES

Staff of the Biomedical Computer Laboratory continue to supervise graduate students and teach formal courses at the School of Medicine and the School of Engineering. In addition, the following non-credit course was conducted by the Laboratory during the past year.

Introductory MUMPS Programming Course for Beginners, Fall 1980.

A high-level programming language (Massachusetts General Hospital Utility Multi-Programming System - MUMPS), especially well suited for medical information systems and other textual and database applications, was presented by Joel Achtenberg, A.B. An Interactive MUMPS teaching program and access to a computer which supports Standard MUMPS were provided for laboratory exercises.

Attending the course were:

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|---|---|
| John Bealke, B.A. | WU Medical Student |
| Monty Brandenberg | WU Engineering Student |
| Abid Eesa-Khalaf | WU Medical Student |
| Cynthia Fedders, B.A., M.S.L.S. | Medical School Library |
| Elizabeth Galie, R.N. | Cardiology |
| Cary Gutbezahl, M.D. | Pathology |
| Toni Hammond | Psychiatry |
| Sumner Holtz, M.D. | Radiology |
| David Levine, B.S.E. | WU Medical Student |
| Yoshiyuki Matsumoto, A.S. | Medical School Library |
| Gene Mueth, B.S. | Medical School Business Office |
| Audrey Powderly, B.A., M.S.L.S. | Medical School Library |
| Debbie Proffer | Biomedical Computer Laboratory |
| Janet Rieders, B.A. | WU Medical Student |
| Al-Emmari Saud | WU Medical Student |
| Ken Schechtman, B.S., M.A., M.S., Ph.D. | Biomedical Computer Laboratory |
| Monica Shieh, M.L.S. | Biomedical Computer Laboratory |
| Zhuang Tian-ge | Biomedical Computer Laboratory |

## VIII. SEMINARS

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

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| "INTEL 8086 Processor and Development Support"<br><br>August 20, 1980 | Mr. Randy Ferber<br>Technical Representatives, Inc.<br>St. Louis, Missouri |
| "M68000 Processor and Development Support"<br><br>August 29, 1980 | Mr. Don Jerich<br>Motorola Systems Sales Manager<br>Motorola Semiconductor Products<br>St. Louis, Missouri |
| "AMD Z8000"<br><br>September 2, 1980 | Mr. Mike Hansen<br>Field Applications Engineer<br>Advanced Micro Devices<br>Chicago, Illinois |
| "Some Mathematical Aspects of Positron Emission Tomography with Time of Flight Measurements"<br><br>November 21, 1980 | Dr. Donald L. Snyder<br>Biomedical Computer Laboratory and<br>Department of Electrical Engineering<br>Washington University<br>St. Louis, Missouri |
| "Spin Alignment in $^{12}C$-$^{12}C$ Inelastic Scattering"<br><br>January 27, 1981 | Dr. Stephen J. Willett<br>Wright Nuclear Structure Laboratory<br>Yale University<br>New Haven, Connecticut |
| "Simulation of Ultrasound in Tomographic Imaging: Theory and Methods Based on Geometrical Acoustics"<br><br>April 17, 1981 | Dr. Gary H. Brandenburger<br>Biomedical Computer Laboratory<br>Washington University<br>St. Louis, Missouri |
| "Rule Governed Stimuli, Processing Strategies and Skilled Behavior: An Hemi-Retinal Approach"<br><br>April 27, 1981 | Mr. Richard Hurtig<br>University of Iowa<br>Iowa City, Iowa |

"NCC '81 Exhibits (or)
"A Random Walk Through McCormick Place"

May 14, 1981

Dr. G. J. Blaine
Mr. R. E. Hitchens
Mr. R. W. Hagen
Biomedical Computer Laboratory
Washington University
St. Louis, Missouri

"Meeting Report on the 35th Annual Meeting of the American EEG Society Comments on Computer Systems and Evoked Potentials"

June 22, 1981

Dr. Harold Shipton
Biomedical Computer Laboratory
Washington University
St. Louis, Missouri

## IX. PUBLICATIONS AND ORAL PRESENTATIONS


Ahumada, G. G., Corr, P. B., and Sobel, B. E., "Accelerated Accumulation of Calcium in Cultured Cardiac Myocytes Exposed to Lysophosphatides," Circulation, vol. 62, no. 4, p. III-113, 1980 (abstract).

Ambos, H. D., Geltman, E. M., Fukuyama, O., and Roberts, R., "Infarct Size a Determinant of the Rate of Evolution and Disappearance of Electrocardiographic Manifestations," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 80-CH1606-3, Williamsburg, Virginia, pp. 281-284, October 22-24, 1980.

Arthur, R. M., "Resolution of Phased Linear Arrays for Ultrasonic Imaging," seminar presented for Washington University Biomedical Engineering Program Series, St. Louis, Missouri, September 20, 1980.

Bell, M. J., Maurer, M. M., Bower, R. J., and Ternberg, J. L., "Surgery in Extremely Low Birth Weight Infants," Pediatric Surgery, in press.

Bergmann, S. R., Lerch, R. A., and Sobel, B. E., "Flow-Independent Characteristics of Externally Detectable Cardiac Kinetics of $^{11}$C-Palmitate," American Journal of Cardiology, vol. 47, p. 414, 1981 (abstract).

Bergman, S. R., Lerch, R. A., and Sobel, B. E., "Non-Invasive Characterization of the Influence of Alpha-Bromopalmitate on Cardiac Fatty Acid Utilization," Federation Proceedings, vol. 40, p. 461, 1981 (abstract).

Blaine, G. J., Carroll, L., Ficke, D., Jaszczak, A., Keyes, J., Mullani, N., Thompson, C., and Williams, C., "Emission Tomography Workshop: Data Acquisition and Processing Archictecture for Multiplanar ECAT," presented at the Symposium and Workshop on Emission Tomography: "Physics, Engineering, Computer Science Aspects and Detector Topics," 28th Annual Meeting of the Society of Nuclear Medicine, Las Vegas, Nevada, June 16-19, 1981.

Blaine, G. J., Ficke, D. C., Hitchens, R. E., and Holmes, T. J., "Data Acquisition Aspects of SUPER-PETT," accepted for presentation at the IEEE Nuclear Science Symposium, San Francisco, California, October 21-23, 1981 (abstract).

Brandenburger, G. H., "Simulation of Ultrasound in Tomographic Imaging: Theory and Methods Based on Geometrical Acoustics," Department of Electrical Engineering, Washington University, St. Louis, Missouri, May 1981 (D.Sc. Dissertation).

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Brandenburger, L. L., Moore, P., Miller, J. P., Thomas, Jr., L. J., and Oliver, G. C., "Development of a Computer-Assisted Follow-Up Methodology for Clinical Research," Proceedings of the Fourth Annual Symposium on Computer Applications in Medical Care," IEEE Catalog No. 80CH1570-1, Washington, D.C., vol. 2, pp. 1037-1043, November 2-5, 1980.

Browder, M. W., Blaine, G. J., Montrose, J. K., Coben, L. A., and Thomas, Jr., L. J., "Visual Evoked Potential: Computer Assisted Acquisition and Processing," Proceedings of the Fourth Annual Symposium on Computer Applications in Medical Care, IEEE Catalog No. 80CH1570-1, Washington, D.C., vol. 2, pp. 1240-1249, November 2-5, 1980.

Braunwald, E., and Sobel, B. E., "Coronary Blood Flow and Myocardial Ischemia," in Heart Disease, E. Braunwald, ed., W. B. Saunders Company, Philadelphia, pp. 1279-1308, 1980.

Cheng, N. C., "Image Reconstruction Technique for Positron Emission Systems with Measurement of Time-Difference Information," Proceedings of the Eighteenth International ISA Biomedical Sciences Instrumentation Symposium, Biomedical Sciences Instrumentation, vol. 17, pp. 27-33, April 1981.

Christlieb, I. Y., and Clark, R. E., "Enhancement of Myocardial Protection by an Intracellular-Like Cardioplegic Solution," Archives of Surgery, vol. 115, pp. 1339-1347, 1980.

Clark, G., Strauss, M. D., and Roberts, R., "Dobutamine Versus Furosemide in Treatment of Cardiac Failure Due to Right Ventricular Infarction," Chest, vol. 77, pp. 220-223, 1980.

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# X. MONOGRAPHS AND WORKING NOTES

The Biomedical Computer Laboratory's Monograph Series was established to systematize the many reports, reprints, program descriptions and other documents written at BCL or supported in part by the Laboratory's facilities or staff.

A forum, much less formal than our monograph series, has been instituted to serve as a repository for materials such as: research notes, system and component documentation, technical survey notes and prepublication drafts. A Working Note File is maintained for access by anyone associated with the Washington University Computer Labs. Distribution for outside use can be made available with the consent of the contributor.

## Monographs

Following is a list of the monographs published by BCL during the past year. Copies of the complete index to the Monograph Series are available on request.

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| 386 | Cox, Jr., J. R.<br>Hermes, R. E.<br>Ripley, K. L. | Performance Evaluation of Ventricular Arrhythmia Detectors | 4/80 |
| 387 | Hermes, R. E.<br>Oliver, G. C. | Use of the American Heart Association Database | 4/80 |
| 388 | Hermes, R. E.<br>Geselowitz, D. B.<br>Oliver, G. C. | Development, Distribution, and Use of the American Heart Association Database for Ventricular Arrhythmia Detector Evaluation | 10/80 |
| 389 | Dunham, J. G. | An Iterative Theory for Code Design | 1/81 |
| 390 | Mullani, N. A.<br>Markham, J.<br>Ter-Pogossian, M. M. | Feasibility of Time-of-Flight Reconstruction in Positron Emission Tomography | 11/80 |
| 391 | Hermes, R. E.<br>Cox, Jr., J. R. | A Methodology for Performance Evaluation of Ventricular Arrhythmia Detectors | 10/80 |

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| 393 | Brandenburger, G. H. | CUTARSYS User's Guide (Preliminary) | 2/81 |
| 394 | Garfield, S. A. | BDOS Reference Manual | 3/81 |
| 395 | Clark, K. W.<br>Rolnitzky, L. M.<br>Miller, J. P.<br>DeCamilla, J. J.<br>Kleiger, R. E.<br>Thanavaro, S.<br>Bigger, J. T. | Ambulatory ECG Analysis Shared by Two Independent Computer Labs in the Multicenter Post-Infarction Program (MPIP) | 10/80 |
| 396 | Clark, K. W.<br>McLear, P. W.<br>Kortas, R. G.<br>Mead, C. N.<br>Thomas, Jr., L. J. | Argus/2H Detection of ST-Segment Changes in Ambulatory ECG Recordings | 10/80 |
| 397 | Brandenburger, G. H. | Simulation of Ultrasound in Tomographic Imaging: Theory and Methods Based on Geometrical Acoustics | 5/81 |
| 398 | Kumar, B.<br>Miller, T. R.<br>Siegel, B. A.<br>Mathias, C. J.<br>Markham, J.<br>Ehrhardt, G. J.<br>Welch, M. J. | Positron Tomographic Imaging of the Liver: $^{68}$GA Iron Hydroxide Colloid | 4/81 |
| 399 | Klepper, J. R.<br>Brandenburger, G. H.<br>Mimbs, J. W.<br>Sobel, B. E. | Application of Phase-Insensitive Detection and Frequency-Dependent Measurements to Computed Ultrasonic Attenuation Tomography | 2/81 |
| 400 | Gray, A. J.<br>Moore, S. M.<br>Stein, D. W. | A User's Guide to the Image Processor Programmer's Workbench | 6/81 |
| 401 | Ter-Pogossian, M. M.<br>Mullani, N. A.<br>Ficke, D. C.<br>Markham, J.<br>Snyder, D. S. | Photon Time-of-Flight-Assisted Positron Emission Tomography | 4/81 |

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| 402 | Moore, S. M.<br>Gray, A. J.<br>Stein, D. W. | A Programmer's Reference Manual For the Image Processor Programmer's Workbench | 8/81 |
| 403 | Raichle, M. E.<br>Larson, K. B. | The Significance of the $NH_3$-$NH_4^+$ Equilibrium on the Passage of $^{13}N$-Ammonia from Blood to Brain: A Distributed Model with Random-Valued Parameters for Regional Residue-Detection Studies of Radiotracer Transport | 6/81 |

## Working Notes

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| 9 | Holmes, T. J. | Mathematical Evaluation of Count Loss Versus Conversion Time for PETT VII | 10/80 |
| 10 | Blaine, G. J. | A Proposal for a Modest Local Area Network Experiment | 2/81 |
| 11 | Shum, Chung-dak | Display Module | 4/81 |
| 12 | Massey, J. S. | Operator Control Panel Documentation Package | 6/81 |