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Progress Report No. 18

Biomedical Computer Laboratory

A

PROGRESS REPORT

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Biomedical Computer Laboratory

Washington University School of Medicine

700 South Euclid Ave.

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BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

PROGRESS REPORT NO. 18

JULY 1, 1981 - JUNE 30, 1982

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I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes activities during the period from July 1, 1981 through June 30, 1982. 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. Perseverance 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 most departmental divisions within 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 from two grants from the National Institutes of Health, Division of Research Resources.

RR 00396 and RR 01380 A Resource for Biomedical Computing.

NHLBI contract NO1 HV 72941 continues to fund a Holter Monitoring Core Laboratory to support a Multicenter Investigation of Limitation of Infarct Size.

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.

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

A Workshop on Time-of-Flight Emission Tomography was funded jointly by the Division of Research Resources and the National Heart, Lung and Blood Institute by grant RR 01358. The workshop was held in May 1982 with additional support being received from the Hamamatsu Corp., Nashua, New Hampshire, Nucletronix, Inc., Gloucester, Massachusetts, and the IEEE Computer Society.

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

Public Health Services grants.

AM 07296 Cell Biological Approaches to Diabetes Research,

AM 20579 Diabetes Research and Training Center,

EY 00256 Factors Affecting Intraocular Pressure,

EY 00258 Cytology and Physiology of the Retina,

EY 02044 Automated Digital Processing of the Human Visual Field,

EY 02687 Center for Vision Research,

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

EY 03703 Chromatic Static Perimetry in the Diagnosis of Glaucoma,

GM 28232 Physical Mapping of Yeast Chromosomal DNA,

HD 09998 Clinical Correlations to Vitamin D Status in Infants,

HL 12839 Erythrocyte Deformability and Vascular Pathophysiology,

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 Tomography for Cardiac Imaging,

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, and Senior Research Associate, Computer Systems Laboratory

Senior Research Associates

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

Business Manager

Virginia M. Bixon, B.S.

Research Associates

Robert J. Arnzen, Ph.D., and Computer Systems Laboratory
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Kenneth W. Clark, M.S.
James G. Dunham, Ph.D., and Associate Professor of Electrical Engineering
Robert O. Gregory, D.Sc., and Professor of Electrical Engineering
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Richard E. Hitchens, B.S., and Lecturer in Computer Science
William F. Holmes, Ph.D., and Associate Professor of Biological Chemistry, and in Computer Science
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 Associate Professor of Medicine

Research Assistants

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Kadagattor V. Gurumurthy, M.S., and in Electrical Engineering
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Margaret C. Jost, M.S.
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J. Stevadson Massey, M.S., and in Neurological Surgery
M. Michael Maurer, Jr., M.D., and Assistant Professor of Pediatrics
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J. Philip Miller, A.B., and Assistant Professor of Biostatistics in Preventive Medicine
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Jill D. Buchholz
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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., Professor of Clinical Medicine
Rexford L. Hill, III, M.S., Assistant Professor of Computer Applications in Radiology
Burton E. Sobel, M.D., Professor of Medicine and Director, Cardiovascular Division

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

Joseph J. Armistead, B.S.
Ricardo G. Kortas, M.D.
Creon Levit
Donald J. Santel
Kou-Hu Tzou, 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.

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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:

Mead Johnson, Pharmaceutical Division, Evansville, Indiana - Collaborative drug study.

International Business Machines (IBM), Biomedical Systems, Hopewell Junction, New York - Digitizing of long-term ECG recordings.

IV. PHYSICAL RESOURCES

The Biomedical Computer Laboratory (BCL) was formed on April 15, 1964 and the original staff moved into 3,800 square feet (net) of laboratory space at 700 South Euclid Avenue in Saint Louis. While remaining at this location, adjacent to the Washington University School of Medicine's main building complex, the floor space has been increased to the present 12,000 square feet (net). In addition to this space, BCL staff members and systems frequently occupy other areas within the Washington University Medical Center at the sites of collaborative project activities. Facilities for staff offices, laboratory areas and computational applications are located within BCL at the Euclid Avenue address. A machine shop and reference room are also located on the premises and shared with a sister laboratory, the Computer Systems Laboratory. 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 analog and digital recording instruments. Systems for use in developing eight-bit, sixteen-bit and bit-slice microprocessor applications are available.

The Laboratory has gradually increased its computing resources 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 was 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. During the past eighteen years BCL has addressed diverse biomedical problems for which digital computing techniques seemed promising and appropriate. Today BCL has interest and involvement in over one hundred minicomputer systems (representing twenty different makes and models) within the Washington University Medical Center. BCL has primary responsibility for 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. Retired last year was an IBM System/7 computer that had been used since 1972 to support an Argus/H arrhythmia analysis system. Following unproductive efforts to find a user for the computer at this institution or elsewhere, it was donated to Creighton University in Omaha where other System/7's are in use for real-time ECG rhythm monitoring.

A local computer network, TERRANET, provides remote terminal-to-computer and inter-computer data communications at rates up to 9600 bps among some seventeen stations located throughout WUCL. At present, TERRANET resources include eight video terminals, eight host processors, and a 300/1200 baud modem. 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 at the BCL. Personal-class microcomputer systems have been incorporated into the design of biomedical research systems and numerous 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. A total of 72 distinct project activities are grouped into the five project areas summarized below.

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. From those studies, a database of 2400 processed 24-hour recordings has been applied to the development of a stochastic model of dysrhythmia occurrences useful for the design of prospective intervention trials. The American Heart Association database for the evaluation of dysrhythmia detectors is now essentially complete and distribution to users has begun. Collaborative studies include two multicenter projects of national scope as well as several antidysrhythmic drug evaluations. 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, radiation-treatment planning, and the development and application of positron emission tomography. Advanced computing techniques are used to study tissue interactions with both transmitted and reflected ultrasound. Discrimination of normal and infarcted myocardium has been achieved. The tissue-characterization work is now supported separately as a BRP resource technology development project. 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 has used macromodules to capitalize on opportunities for parallelism in the computations and applies the MMS-X system for display of the three-dimensional isodose contours. Current emphasis is on the development of a custom-designed large-scale integrated circuit for practical realization of the method. The work capitalizes on our close ties with the Computer Systems Laboratory. 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. Specialized hardware is being developed to process the time-of-flight information. Under separate support from DRR and NHLBI, an International Workshop on Time-of-Flight Emission Tomography was organized and hosted at this Resource. 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. Work on DNA restriction mapping studies with the Department of Genetics has moved forward with a redesign and now implementation of the system for automated reading of electrophoretic gels and the development of a probabilistic model which has assisted in the design of study protocols. Collaborations with the Department of Ophthalmology include completion of a system for constant-area tonography to study the dynamics of fluid flow in the canal of Schlemm. Other collaborations with ophthalmology include the computer-assisted acquisition and analysis of visual field data and continuing work on 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 have supported 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 under independent support. For the developed databases, efforts in the past year have been directed to developing independent user funding.

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. Expansion 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 4.2 kilometers away; and toward the development and now deployment 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 cross-assemblers, cross-compilers, development-station consoles, logic analyzers, and a library of system modules. New work with the Department of Radiology is developing a comprehensive approach to a system for digital radiology studies.

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 supported collaborations which address other aspects of ischemic heart disease, such as myocardial metabolism and blood flow, the electrophysiologic characterization of abnormal myocardial depolarization, and various anti-dysrhythmic drug studies.

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 multi-center clinical studies of interventions to limit infarct size and of post-infarction risk stratification. The substantial database of processing results accumulated from those studies has been used to develop a stochastic model of dysrhythmia occurrences useful to the design of intervention trials. The systems also provide the power and flexibility necessary for work on algorithm revision and on new signal-processing strategies and they have further served 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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Support: RR 00396
RR 01380
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Continued algorithm development seeks faster and better ways to extract clinically-revelant information from tape-recorded electrocardiograms (ECGs). Development continues in both frequency-domain and the time-domain algorithms. Frequency-domain algorithms, reported elsewhere (A-2), show great promise but must be evaluated for hardware implementation to demonstrate efficiency. Time-domain development has focused upon supraventricular arrhythmia detection, two-channel analysis, and microprocessor implementation of proven algorithms.

Supraventricular arrhythmia analysis. Early work in this area was hampered by lack of an annotated database of supraventricular arrhythmias. A collection of 100 annotated one-hour segments has alleviated this problem. This dataset provided the basis for an evaluation of an algorithm for detection of supraventricular premature contractions (SPCs). Meanwhile, the collection continues to expand as more interesting and challenging waveforms are found.

For that collection, one-hour records were extracted from 100 24-hour recordings from a single study. The one-hour segments were chosen to include at least one of the following phenomena: SPC rate greater than 6 per minute, SPC couplets or runs, supraventricular bigeminy, paroxysmal supraventricular tachycardia, atrial fibrillation, 2nd or 3rd degree AV block, or wide R-R variations. Each one-hour segment was annotated, beat-by-beat, in machine-readable form to facilitate evaluation. The dataset included 471,519 beats of which 5153 were premature ventricular contractions and 4400 were SPCs. SPCs occurred in 81 records, SPC couplets in 23, and SPC runs in 49 records. Atrial fibrillation appeared in 7 records. In 56 records, none including atrial fibrillation, heart rate range exceeded 30 beats per minute.

In a preliminary SPC-detection evaluation using this dataset, the SPC-detection logic captured 95% SPCs, 86% SPC couplets, and 98% SPC runs. The overall false positive rate was less than 1%. The evaluation suggested several improvements to the SPC-detection logic which would improve the true-positive rate and lower the false-positive rate. While these and other improvements are being implemented, additional waveforms are being added to the dataset.

Two channel ECG analysis. Although long-term ECG recordings typically include the ECG signal from two surface-electrode leads and the Argus/2H system digitizes both, the Argus dysrhythmia algorithms analyze only one lead (channel). Although either channel may be analyzed and either is sufficient for a great majority of signals, there are certain times when analysis of both channels would be helpful: artifact, signal dropout, bizarre waveforms, and waveforms which are abnormal in one channel but which mimic the normal complex in the analysis channel.

Prior to the advent of microprocessors, the task of analyzing both channels was much too expensive since multiple passes through the recording by the same processor or parallel analysis by dual processors would be required (actually, Argus/2H uses 2 processors but one digitizes while the other analyzes). Microprocessors now provide a cost-effective solution for parallel processing. While hardware configurations are under consideration, we are developing a software algorithm for comparing the outputs of the analyses of separate channels. These outputs are beat labels with their occurrence times and morphological measurements; the arbitration algorithm would assign final labels. Further development and evaluation of the algorithm will hopefully demonstrate that the data stream of final labels is superior to either of the original label streams. Lessons gained from this investigation and from work in the frequency domain (A-2) may shape the hardware configuration for a microprocessor-based Argus/2H.

Microprocessor implementation. In addition to continued algorithm improvements, efforts are underway to process tape-recorded ECGs faster. Broad local interest in the Motorola 68000 microprocessor prompted implementation of the Argus algorithms and their improvements on the 68000 processor. The PDP-11/34 RSX system (E-3) provides an excellent program-preparation facility for this development work. Although the core algorithms have been coded and partially debugged, timing marks are not yet available for comparison with previous implementations. A planned data link to one of the Argus/2H arrhythmia analysis systems will facilitate access to a large number and variety of waveforms.

A-2. Frequency-Domain-Based Analysis of the ECG

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During the past four years we have been examining frequency-domain (FD) analysis of the ECG with the goal of deriving a set of parameters useful in ECG pattern recognition. Although an ECG classification system based entirely in the FD could conceivably result from such investigations, our immediate focus has been the utilization of FD information as an adjunct to more traditional time-domain (TD) analysis. Specifically, TD processing approached via either feature extraction (as in the BCL-based Argus system) or correlation strategies contains an inherent fiducial-point (position) dependence which can be troublesome when certain waveforms are encountered (e.g. conduction defects or signals embedded in high-frequency, low-amplitude base-line noise). FD analysis offers the attractive theoretical possibility of separation of a waveform's morphology from its fiducial point per se via analysis of the signal's amplitude (or power) spectrum rather than the entire amplitude plus phase (position) spectrum. Obviously, complete disregard for phase information contains its own particular pitfalls such as the inability to distinguish between mirror-image waveforms; our efforts have therefore been directed at a carefully controlled application of FD information.

We have described a FD-based algorithm for distinguishing Normal from Non-Normal waveforms (PR 17, A-4). Basically, the algorithm examines all Non-Normal (as classified by Argus) complexes by means of a standard FFT computed over 512 ms of context (chosen to include the entire PQRST complex). Only Argus Non-Normal waveforms are examined because of the highly accurate assignment of the Normal label by Argus. The population of Argus Non-Normal waveforms includes PVCs and abnormal beats which are not PVCs as well as noise-contaminated and/or mismeasured Normals. A 3-level decision hierarchy is used to compare each candidate Non-Normal to a suitable "local" Normal waveform. Level 1 consists of an initial screening of beats as "possibly Normal" using a standard correlation coefficient calculated on the two complexes' FTs (FDCC). The "sameness" threshold for the FDCC is, however, set substantially lower ($r>.7$) than what would be acceptable in a stand-alone correlation system ($r>.9$). Waveforms passed to level 1 ($r>.7$) which are not identical in shape ($r<.95$) are passed to levels 2 and 3 for examination via several fiducial-point-insensitive FD parameters extracted from the signals' amplitude-normalized power spectra. However, the FDCC threshold of .7 modulates the inherent dangers of sorting waveforms via only amplitude-spectral data by reliably separating waveforms with gross morphological differences which would appear similar if only amplitude data were considered

(e.g. mirror-image waveforms). Differences or similarities in waveform morphology subsequently detected in levels 2 and 3 are thus quite reliable. The parameters utilized in levels 2 and 3 are: two correlation coefficients computed on two power "sub spectra" (2-12 Hz and 10-30 Hz) and four power spectra shape descriptors (first spectral moment (FSM) 2-30 Hz, FSM 2-12 Hz, FSM 10-30 Hz, and spectral dispersion 2-30 Hz).

The single largest advantage of the fiducial-point insensitive FD approach is its ease of applicability to intermittent processing of the second channel of recorded ECG data (currently Argus processes only a single channel of ECG data because of time constraints). Beat delineation markers from channel 1 may simply be "mapped" into channel 2 without concern for inter-channel beat onset and/or termination variability secondary to electrode placement or recording-head skew. Experience has shown that the power spectral shape parameters will tolerate up to 25 ms of fiducial point jitter without a degradation in performance. The ease of second channel analysis substantially increases the reliability of the waveform classification algorithm because of the relatively rare occurrence of simultaneous bi-channel noise.

The FD-based algorithm for sorting Normal and Non-Normal complexes was successfully evaluated and presented at the 1981 session of Computers in Cardiology.[1] During the past year, the logic has been expanded to include PVC detection using a catalog-based learning strategy similar to that previously described for Machine Edit.[2] Specifically, a catalog of 2-channel sample and FFT data for the eight most recently encountered Non-Normal morphologies is maintained. Each time a new Non-Normal waveform is encountered, an attempt is made to place it in one of the already established catalog families using the 3-level FD algorithm described above. Each beat placed in a family is signal-averaged with the running family average to maintain an evolving family template. Only the channel in which a family fit occurred is averaged, thereby preventing the corruption of the template by noisy signals. Families may be labeled as "true-PVC family" if individual members are verified as true-PVCs based on morphological and contextual timing data. All subsequent beats placed in such a family are labeled true-PVC regardless of timing, thereby allowing for the automatic labeling of fusion PVCs and those that occur in couplets or runs. The assignment of the "true-PVC" label to a family invokes a propagation algorithm which labels as "true-PVC family" all families sufficiently close of the established true-PVC family with respect to the FD metrics. The processing of candidate true-PVCs does differ somewhat from that of candidate Normals in that beats are realigned with a centroid calculation if initial attempts to place them in an existing family based on the Argus-determined onset as the beat's fiducial point should fail. This somewhat computationally costly change was necessitated when it was discovered that the generally larger amplitude, bizzarely shaped PVC morphologies had Argus fiducial-point inaccuracies of 30-50 ms, in excess of that tolerated by the FD algorithm. The presence of this realignment logic does not, however, degrade the conceptual framework of the algorithm which provided a useful synthesis of correlation and feature-extraction approaches combined with a degree of fiducial-point independence.

Evaluation of the algorithm has centered around two separate issues: first, a performance evaluation of a software version of the algorithm, and second (assuming favorable algorithmic performance), a feasibility study to explore the possible processing strategies and hardware architectures suitable for implementing the algorithm in the 60-times-real-time Argus/2H processing environment. With respect to the software evaluation, initial results on selected tapes separate from the algorithm's training set have been extremely encouraging and suggest an order-of-magnitude increase in automated PVC and Normal waveform classification over traditional Argus. The recent availability of the AHA database (A-4) provides a suitably challenging database on which a more extensive evaluation can be conducted. The hardware feasibility of the algorithm is being investigated for the various computationally intensive portions (e.g. correlation, FFT, FSM, etc.). Because the algorithm processes only Argus Non-Normal waveforms, (at worst case only about 25% of all the waveforms on a given tape), it can run as a background process at substantially slower rates than that required of Aztec, Primitive, and Cycle. Initial theoretical analysis of the algorithm's processing requirements strongly suggests that, from the menu of off-the-shelf chips, specially designed and/or distributed processors, or VLSI technology, a cost-effective hardware implementation of the algorithm seems reasonable. Design studies of such an implementation will be the central focus of our work during the coming year.

1. C. N. Mead, H. R. Pull, J-S. Cheng, K. W. Clark, and L. J. Thomas, Jr., "A Frequency-Domain-Based QRS Classification Algorithm," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 81CH1750-9, Florence, Italy, pp. 351-354, September 23-25, 1981.

2. C. N. Mead, K. W. Clark, G. C. Oliver, and L. J. Thomas, Jr., "Progress Toward Fully Automated Processing of Ambulatory ECGs," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 76CH1160-1C, St. Louis, Missouri, pp. 183-188, October 7-9, 1976.

A-3. Processing of Long-term ECG Recordings

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In addition to Argus algorithm development (A-1, A-4), the two Argus/2H arrhythmia analysis systems are used to process long-term (Holter) ECG recordings for three studies: the Multicenter Investigation of the Limitation of Infarct Size (A-12), 1538 recordings processed; a clinical trial of nifedipine in cardioplegia (A-13), 326 recordings; and a Mead Johnson sponsored study of the antiarrhythmic drug Encainide (VI, Industrial Collaboration), 189 recordings. Argus/2H analysis protocols for these studies have been previously described (PR 15, A-4).

A-4. American Heart Association Database

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The final phases of development of the American Heart Association Database have been implemented during the past year. Previous reports (PR 16, A-8; PR 17, A-5) have detailed the effort involved in collecting data for the database. Recent progress has been made in finalizing each database tape, dividing the tapes in each class into test and development sets, and distributing the tapes.

Reconciliation of annotations for each database tape has been a tedious and time consuming process to which much effort was devoted. This process involved comparing the beat annotations of each database annotator to yield a final set of annotations which was agreeable to all. Once annotations for each tape were reconciled, the process of merging the final annotation set with the sampled ECG waveform data, verifying beat onsets, and generating hardcopy printouts of each tape was undertaken. Merging beat annotations to the actual events on each

tape is an automated process, however it was also necessary to manually verify every beat onset in each annotated 30 minute tape segment. A hardcopy plot of each tape was generated on a Versatec plotter. Each plot consists of the ECG waveform, the event annotation stream, and an event number.

At this time six of the eight database classes are finished and distribution of these tapes has begun. The completed database tapes were duplicated for delivery to the official database distributor, ECRI of Plymouth Meeting, PA. ECRI was provided with sets of the long and short versions of the completed database including the hardcopy printout. ECRI has received many orders for the database and, at present, has delivered eleven complete sets.

Work is still underway to complete the remaining two classes which have been particularly troublesome due to the infrequent occurrence of these arrhythmias (R-on-T and Ventricular Fibrillation) on ambulatory recordings. A strategy for completing these classes has been implemented so that completion of the last two classes can be assured within the next few months.

A-5. Performance Evaluation of Ventricular Arrhythmia Detectors

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Significant progress has been made toward development of a performance parameter for reporting the correct detection performance of automated ventricular arrhythmia detectors. Last year's report (PR 17, A-6) highlighted the development of a performance parameter. Recent work has pursued the derivation of a bound on the estimation error for the performance parameter.

A correct detection performance parameter was developed and is a function of the number of tapes, number of PVC annotations, and number of PVC detections in an ECG test database. Determination of an error bound on the estimation parameter is a very significant development since it is useful for determining the accuracy of the estimator and useful in evaluation-database design. Initial attempts at deriving the Cramer-Rao bound for the estimator were fruitless because of the intractability of the mathematics. More insight into the problem was gained through simulation of the estimator, where it was found that a simpler bound could be derived from a simple average-detection-ratio estimator. Further study resulted in drivation of a bound on the variance of the estimator

$\hat{p}$ where $\hat{p} = \hat{\alpha}/\hat{\alpha}+1$ and where $\hat{\alpha}$ is the maximum likelihood estimation parameter. The bound is a function of the number of tapes in a database, the estimator $\hat{\alpha}$, and the average database event rate. This bound has been incorporated into a more useful bound on the mean squared error. A set of curves has been generated which can be used to determine the error bound for most situations.

The development of the estimator and error bound for the correct detection case is nearly complete. Future work may include development of a similar estimator for reporting the false detection rate of an automated detector, as well as extension of this modeling technique to other types of event detectors.

A-6. Fast Fourier Transform Analysis of Signal-Averaged ECG Complexes

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This project was undertaken to non-invasively identify patients at risk for malignant dysrhythmias, such as reentrant ventricular tachycardia by employing fast fourier transform (FFT) analysis on the terminal part of the QRS and ST-T wave portions of the surface ECG. In the last few years, late activation potentials have been recorded with signal-averaging techniques in patients with ischemic heart disease.[1-3] These signals were coincident with the QRS and usually occurred 40 to 200 ms after the onset of the QRS complex. All of these studies were done in the time domain utilizing digital filters and high-gain amplifiers. In order to avoid problems with filter artifacts, we decided to employ the FFT and analyze the resulting frequency-domain data.

To accomplish data collection and analysis, we use a Digital Equipment VT 103-LSI 11/23 microcomputer equipped with 64 Kbytes of memory, 2 serial ports, a dual floppy disk system, 16-channel analog-to-digital converter and a Selanar raster graphics board. The bipolar X, Y, and Z leads are recorded via a HP 1507A vectorcardiograph and digitized at 1000 samples/second.

Using a template recognition program, only normal beats are averaged, i.e. all abnormal and post abnormal beats are rejected. One hundred to 150 normal beats are averaged and stored on floppy disk. Presently, all analysis is done off-line but in the near future we hope to do the data acquisition, averaging and FFT analysis on-line.

1. J. J. Rozanski, J. Myerburg, and A. Castellanos, "A New ECG Waveform Identified by Signal Averaging in Patients with Recurrent Ventricular Tachycardia," Circulation, vol. 60, no. 4, p. II-22, 1979 (abstract).

2. G. Breithardt, R. Becker, and L. Seipel, "Non-invasive Recordings of Late Ventricular Activation in Man," Circulation, vol. 62, no. 4, p. III-320, 1980 (abstract).

3. M. B. Simson, "Use of Signals in the Terminal QRS Complex to Identify Patients with Ventricular Tachycardia after Myocardial Infarction," Circulation, vol. 64, pp. 235-241, 1981.

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

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We have continued our previously reported studies (PR 15, A-10; PR 16, A-10; PR 17, A-7) of the pathophysiology of ischemic injury to the heart. To define relationships between the duration of severe ischemia and microvascular functional integrity with an approach potentially applicable to studies in vivo, the effects of 30 min and 60 min of global, no-flow ischemia on the coronary vasculature of isolated, perfused rabbit hearts were determined. Residue-detection data, analyzed with a two-compartment model, were used to estimate indices of microvascular function, including the mean-transit time ($\bar{t}_{BSA}$) of radiolabeled bovine serum albumin (^{125}I-BSA), vascular into extravascular-space clearance (F_{21}), and vascular- (V_1) and extravascular- (V_2) space volumes. It was shown that the Central-Volume Principle of tracer kinetics does not hold when transport of label between vascular and extravascular spaces takes place convectively by

solvent drag, and a more general expression for $\bar{t}_{BSA}$ was derived and applied. Left-ventricular (LV) end-diastolic pressure (LVEDP) and LV developed pressure were monitored with an isovolumic balloon. Aortic perfusion pressure, LVEDP, LV developed pressure and V_1 remained constant, while $\bar{t}_{BSA}$, F_{21} and V_2 increase gradually during 3-hour control perfusions. Perfusion pressure, $\bar{t}_{BSA}$ and F_{21} increased significantly with reperfusion after 30 min of ischemia even though LVEDP and LV developed pressure returned to control levels. V_1 increased minimally while V_2 increased 5-fold during reperfusion. These changes in ^{125}I-BSA washout and permeation across endothelium with reperfusion after no-flow ischemia indicate that compromised vascular integrity is an early manifestation of ischemia with functional consequences that persist even after ischemia sufficiently brief to permit restoration of left ventricular performance.

A-8. Modification of Infarct Size

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Support: RR 00396
RR 01380
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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 myocardial infarction. Infarct size was estimated from serial plasma creatine kinase (CK) changes during a 72-hour interval and by serial positron emission transaxial tomographs, and results in controls were compared to those observed in the treated group. All Holter tapes were digitized and processed by the Argus/2H computer system. Left and right ventricular function was assessed by radionuclide ventriculograms before and after therapy.

The prospective study initiated in 1978 to assess the effect of intravenous nitroglycerin in patients with acute myocardial infarction was recently completed. The study was performed to assess the safety of administration of intravenous nitroglycerin to patients with acute infarction under conventional clinical conditions, i.e., without the use of hemodynamic monitoring and to determine prospectively its effect on myocardial infarction size assessed by serial determinations of plasma creatine kinase. One hundred fourteen patients were prospectively enrolled in the randomized trial on the basis of a history of chest pain and electrocardiographic changes suggestive of acute infarction. Patients were excluded if systolic blood pressure was less than 100 mm hg, heart rate was greater than 120 beats per minute, if symptoms occurred more than 10 hours prior to admission, or specific anti-hypertensive therapy was mandated. This restricted the patients admitted predominately to patients in clinical class one or two. In treated patients the mean time to initiation of therapy was 6.0 hours. Eighty percent of the treated patient group had a 10% reduction in blood pressure as the end point of titration. Hypotension occurred in six patients but was rapidly reversed with fluids plus atropine in a small subset. Of 114 patients enrolled in the study, 85 suffered acute myocardial infarction, 43 in the treated and 42 in the control group. There were no differences in the demographic characteristics of these groups with respect to age, sex, locus of infarction, clinical class or the incidence of previous infarction. Infarct size (see Figure 1) tended to be smaller in patients receiving intravenous nitroglycerin (11.2 ± 2.1 ck/gm eq/m^2 compared to 14.9 ± 2.1 ck/gm eq/m^2) but this trend did not reach statistical significance (P=.06). This trend was due to differences in patients with inferior myocardial infarction. Infarct size in the control patients was 19.1 ± 3.6 compared to 12.2 ± 1.8 ck/gm eq/m^2 in treated patients (P=.05). A similar trend occurred in patients with subendocardial infarction, however, the sample size was too small for the effects to reach statistical significance. Infarct size was nearly identical in treated and control patients with anterior infarction. In addition, there was no difference in morphine requirements during the first twenty-four hours. The treated patients received 11.4 ± 1.8 mg compared to $12. \pm 2.2$ mg in control patients. Patients in the treated group received a comparable amount of lidocaine compared to controls (1692 ± 250 mg compared to 1512 ± 232 mg). PVC's were more frequent in the treated than the control group but not statistically significantly so. These data lead to two important conclusions. First, intravenous nitroglycerin seems to be associated with salvage of ischemic myocardium in patients with inferior myocardial infarction. The reasons for this are not clear but given experimental data which suggest that infarct size is not reduced in animal models after coronary ligation, we would hypothesize that this change may be due to coronary vasospasm, an increased incidence of which occurs in distribution of the right coronary artery. Second, morphine requirements were not altered by the use of intravenous nitroglycerin. This data represents the first prospective and controlled evaluation of intravenous nitroglycerin as an analgesic in patients with myocardial infarction.

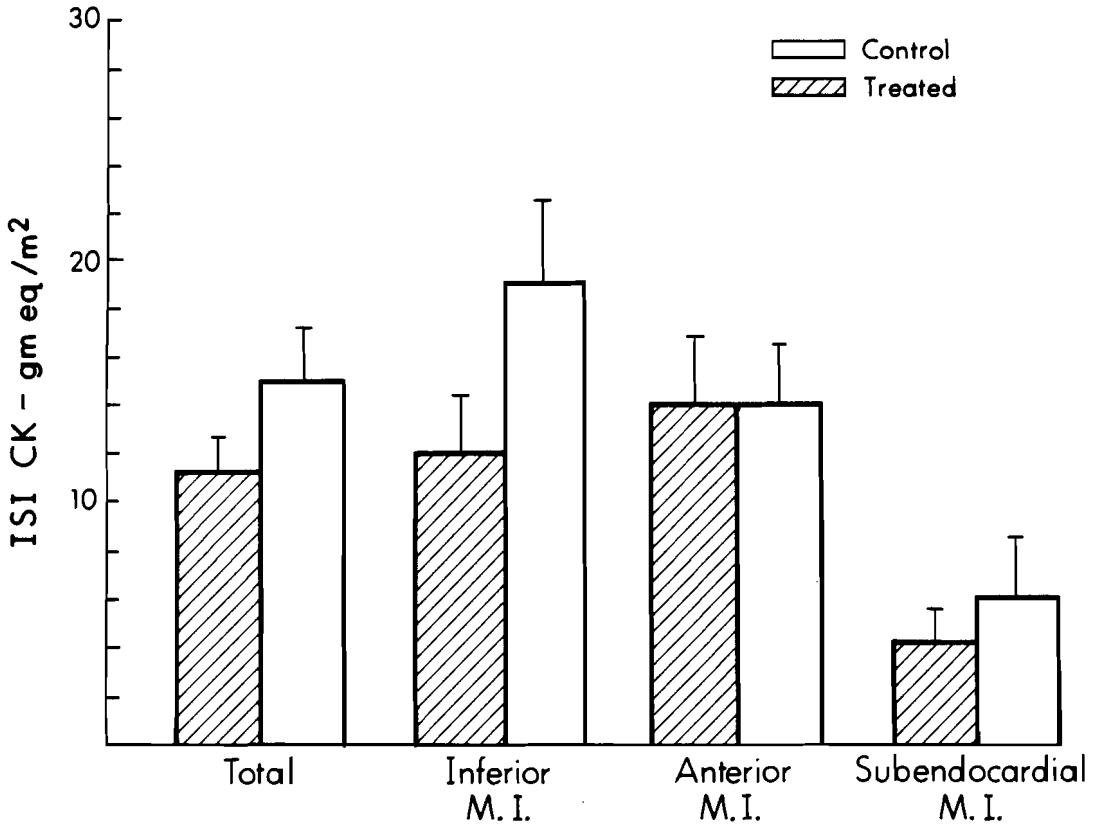

Figure 1. Shown here in graphic form is infarct size in control and nitroglycerin treated patients. Control patients are designated by the open bars and treated patients by the cross-hatched bars. Infarct size index is plotted on the ordinate and infarct location on the abscissa. There was a trend toward reduced infarct size in nitroglycerin treated patients for the entire group; infarct size in this group measured 14.9 ± 2.9 (SE) ck/gm/eq per m^2 compared to 11.2 ± 2.1 ck/gm/eq per m^2 in treated patients. As depicted graphically, this trend was due predominately to a reduction in infarct size in patients with inferior myocardial infarction who were treated with nitroglycerin. Infarct size in the treated patients with inferior myocardial infarction was 12.2 ± 1.8 compared to 19.1 ± 3.6 in controls. This difference was statistically significant, $P=.05$. The difference in patients with subendocardial infarction were not statistically significant due to the small number of patients evaluated with this locus of infarction. Infarct size index was identical in treated and control patients with anterior myocardial infarction.

Other investigations concerning the effects of pharmacologic therapy on infarct size have utilized serial evaluations by positron emission transaxial tomography (PETT) (PR 17, B-10). Positron emission tomography allows for the assessment of an initial area of biochemical abnormality with subsequent delineation of the change in such an area after therapy. This technique has been utilized to evaluate the effects of nifedipine in 10 patients admitted to the Barnes Hospital Coronary Care Unit with suspected acute myocardial infarction. Patients were enrolled if the diagnosis of acute myocardial infarction was suggested by a cardiac origin of chest discomfort, electrocardiogram, and serial elevations in plasma MB CK activity. Patients eligible for the nifedipine investigation received radionuclide ventriculography and a positron emission transaxial tomograph with ^{11}C-palmitate to define the area of biochemical abnormality. Subsequently, patients were randomized to nifedipine at a dose of 20 mg every four hours or placebo. Repeat radionuclide ventriculographic studies, serial determinations of plasma MB CK for determination of enzymatic infarct size, acute Holter monitoring and repeat positron emission tomography at 10 days was accomplished. We previously have documented the safety and hemodynamic benefit of nifedipine in patients with acute myocardial infarction.

Twenty nine patients were randomized to this study, ten undergoing PETT evaluation. Sixteen of the 29 patients received nifedipine. Nifedipine treatment was initiated at the mean of eight and one-half hours after onset of symptoms (range 3 to 18). Side effects in placebo and nifedipine treated groups were comparable with respect to nausea, vomiting and hypotension. In general, however, hypotensive patients receiving nifedipine were found to have low filling pressures whereas patients with hypotension in the placebo group tended to have elevated filling pressures and recurrent chest discomfort. Nifedipine did not affect the amount of morphine sulfate required during the first 24 hours for control of pain (12. $\pm$ 3.6 mg compared to 13.4 $\pm$ 3.6 mg) in control patients. Hemodynamics tended to improve with nifedipine but, because of the large degree of variability, did not reach statistical significance. In patients receiving nifedipine, ejection fraction increased by a mean of .8 $\pm$ 6.2 units (left ventricle) and .56 $\pm$ 13.7 ejection fraction units (right ventricle) over the first 90 minutes. In contrast, patients receiving a placebo had reductions in left ventricular ejection fraction of 1.3 $\pm$ 8.2 units for the left ventricle and 3.5 $\pm$ 7.8 units for the right ventricle. These changes tended to persist. Enzymatically estimated infarct sizes between the two groups were comparable. Patients receiving nifedipine had an infarct size index of 20.4 $\pm$ 4.6 ck/gm eq/m^2 compared to 18.7 $\pm$ 6.6 ck/gm eq/m^2 in control patients.

There were no differences in PETT-defect scores seen between patients in control and treated groups. Infarct size was 83.6 $\pm$ 16 PETT gm equivalents at the time of initial study and 78.2 $\pm$ 17.6 at time of repeat evaluation. In two patients the size of the defect was diminished by more than 20% and in one patient the defect was 20% larger at 10 days. The 6% mean reduction in infarct size is not different from that observed in control patients receiving placebo where study is included as part of the natural

history evaluation. It is of interest to note that patients receiving nifedipine had a reduction in the incidence of post-myocardial-infarction chest discomfort with only one patient having a solitary episode of pain. In control patients, half of the subjects had multiple episodes of recurrent chest discomfort. The ongoing study suggests that despite beneficial effects on the incidence of post infarction angina and hemodynamics that nifedipine does not have a dramatic effect on infarct size. However, more patient studies would be necessary to reach a definitive conclusion.

A similar approach has been taken to evaluate the time-window during which streptokinase administration may benefit patients with acute myocardial infarction. The approach has been to obtain a PETT study prior to cardiac catheterization and thrombolytic therapy and then after recanalization.

To date, 14 patients have undergone positron emission tomography and proceeded to the Cardiac Catheterization Laboratory. In four patients, anatomy has been appropriate for clot lysis. The ten patients not appropriate for clot lysis are included in the report of natural history studies. In the four patients who underwent successful recanalization (see Figure 2), infarct size was diminished by 30% in three individuals and was unchanged in one. When clot lysis was accomplished within eight hours of the onset of chest discomfort, salutory effects were seen in the area of biochemical abnormality. In the one patient who underwent late thrombolysis, (18 hours) there was no difference in the size of the biochemical abnormality. These studies are continuing in an attempt to define the time-window appropriate for the use of thrombolytic therapy and the impact of such therapy on the progression of ischemic injury. We are optimistic that such studies will provide definitive information. This investigation also holds promise for clarifying the role of creatine-kinase-determined infarct size in patients undergoing thrombolysis.

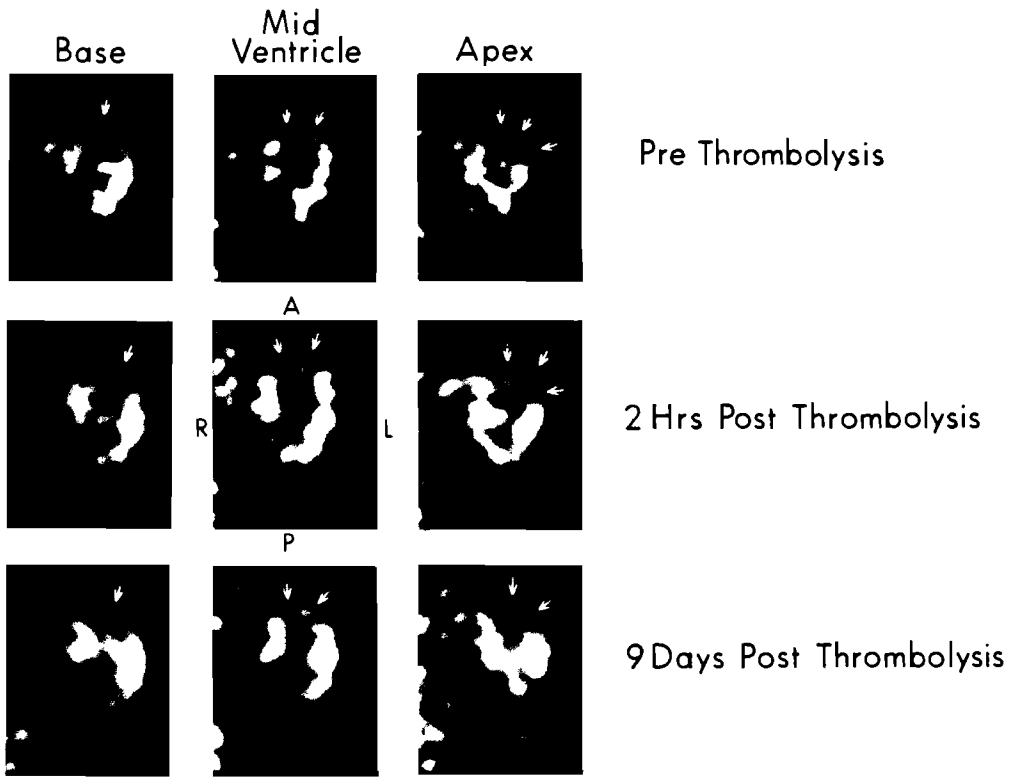

Figure 2. The effect of thrombolysis on the area of biochemical abnormality defined by positron emission tomography is shown. Three representative slices from the fourteen slices imaged are portrayed, one from the base, one from the midventricular level and one from the apex. A=anterior, P=posterior, R=right and L=left. The area of biochemical abnormality noted on the initial image is indicated by the arrows. As can be seen, after recanalization here was reduction in the area of biochemical abnormality. This reduction persisted at nine days. Recanalization in this patient occurred approximately eight hours after the onset of chest discomfort.

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

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HL 17646
AHA 81-108

The overall purpose of these studies is the correlation of electrophysiological derangements with 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. 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. Studies have been completed demonstrating a major electrophysiological role of α-adrenergic stimulation during both coronary occlusion and reperfusion. More recently, we have demonstrated, using radioligand binding, a two-fold reversible increase in α-adrenergic receptors in ischemic myocardium. 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.

Since reperfusion of ischemic myocardium is associated with large increases in total myocardial calcium (Ca^{+2}) and since reperfusion is also associated with enhanced α-adrenergic responsivity and increased α_1-adrenergic receptor number, a recently completed study was performed to determine possible interactions between α-adrenergic receptors and myocardial calcium during reperfusion.[1] Cats were subjected to 35 minutes of LAD occlusion and 10 minutes of reperfusion. Total myocardial calcium was measured by atomic absorption and intracellular calcium calculated using measurements of extracellular space (^{3}H-inulin). In untreated animals, total tissue calcium increased from .32 $\pm$ .05 to .65 $\pm$ .05 (mmol/100 g dry tissue, $p<.0001$) while intracellular calcium increased from .15 $\pm$ .03 to .40 $\pm$ .05 mmol/100 g dry tissue ($p<.001$). Pretreatment with the α-blockers, phentolamine or prazosin prevented the increase

in total and intracellular calcium. Phentolamine and the α_1-adrenergic antagonist BE-2254 given every 2 minutes prior to reperfusion but after ischemia similarly blocked the increase in calcium. β-blockade with propranolol attenuated but did not prevent an increase in total tissue calcium. Electron microscopy with pyroantimonate demonstrated a calcium precipitate in mitochondria of control animals. Though α-adrenergic blockade prevented calcium deposition in mitochondria, other criteria of injury persisted. In addition, the interaction between α-adrenergic receptors and calcium antagonists was studied using radioligand binding procedures. α_1-adrenergic receptors were characterized in rat myocardial membrane preparations using ^{3}H-prazosin. Verapamil, nifedipine and diltiazem were all shown to bind to α_1-adrenergic receptors but with different K_Is of 4.8×10^{-7} M for verapamil, 3.8×10^{-6} for nifedipine and 7.1×10^{-6} M for diltiazem. At conventional doses, only verapamil would be expected to induce potent α_1-adrenergic blockade and thereby may explain its differential antiarrhythmic effectiveness during ischemia and reperfusion in vivo. Thus, α-adrenergic blockade prevents the increase in mitochondrial calcium on myocardial reperfusion. The interaction between calcium antagonists and α_1-adrenergic receptors is further support that α-receptors modulate myocardial calcium particularly during reperfusion and has implications not only for arrhythmogenesis but also myocardial preservation following reperfusion.

A recently completed study was performed to assess the relative β- and α-adrenergic blocking potency of labetalol in the chloralose-anesthetized cat and correlate this to antiarrhythmic efficacy during LAD coronary occlusion for 35 minutes followed by reperfusion.[2] Based on the dose ratio$_{10}$ (DR_{10}) for isoproterenol-induced tachycardia (β) and phenylephrine-induced increase in mean systemic arterial pressure (α), labetalol was 3.1 times less potent than d,l-propranolol (β) and 6.5 times less potent than phentolamine (α). Labetalol was found to be 11.5 times more potent as a β-adrenergic blocking agent than as an α-adrenergic blocking agent. Labetalol (1 mg/kg) failed to significantly reduce either the number of premature ventricular complexes (PVCs) or incidence of ventricular fibrillation (VF) during occlusion (821 ± 150 to 852 ± 246 PVCs and 31% to 20% VF) or reperfusion. In contrast, labetalol at 2 mg/kg and 5 mg/kg significantly ($P<.05$) reduced the number of PVCs during occlusion (320 ± 94 and 466 ± 137, respectively) as well as the incidence of VF (9% and 7%, respectively). During reperfusion, labetalol (5 mg/kg) failed to reduce the number of PVCs but abolished mortality due to VF. The antifibrillatory effect of labetalol, an agent well-tolerated clinically, induces profound antiarrhythmic effectiveness during both experimental myocardial ischemia and reperfusion and may prove to be an effective agent in the prevention and treatment of malignant ventricular dysrhythmia associated with acute myocardial infarction in man.

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. 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, implicating this amphiphilic metabolite as one potential biochemical mediator of malignant dysrhythmia associated with ischemia.[3] More recently, we have demonstrated that LPC increases two-fold in effluents from ischemic feline myocardium in vivo within 10 minutes of coronary occlusion.[4] 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.[4] Additional studies have demonstrated that the arrhythmogenic effects of LPC increase 3-fold in the presence of concomitant acidosis (pH = 6.7).[5] Thus, the concomitant effects of acidosis and accumulation of arrhythmogenic metabolites such as lysophosphoglycerides may be a primary progenitor of 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.[6] More recently, we have completed studies which demonstrate (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 analogous electrophysiological derangements in vitro.[7]

We have recently completed an extensive series of studies 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).[8] In these studies, 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). 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.[8]

To accurately describe the complex electrical activity of in vivo myocardial activation, a computer based, multi-electrode automated mapping system has been developed. This system will be used in experimental animal research aimed at elucidating the basic mechanisms of dysrhythmias associated with myocardial ischemia and reperfusion as well as the role of the adrenergic nervous system. Studies will also be performed in humans during cardiac surgery to localize the activation sequence responsible for dysrhythmias in patients unresponsive to pharmacologic intervention and in localizing accessory pathways of activation in cases of pre-excitation. The system as designed entails differential amplification of up to 240 simultaneous bipolar electrodes with each front end electromagnetically isolated from ground providing less than 10 μA leakage current and fully protected from cardioversion potentials up to 5000V p-p. Each amplifier further contains high-pass filter flexibility with switch selectable filters (3 dB point) of DC, 5 Hz or 40 Hz, and a low pass filter fixed at 500 Hz (3 dB), sample and hold amplification, 12-bit analog-to-digital (A/D) conversion and 12-bit memory. These functions are packaged on a 3" × 12" printed circuit card designed in our laboratory, and 240 of these amplifiers fit in 52" of a standard 19" rack.

The A/D conversion occurs currently at a 2-KHz sampling rate. The output of each channel (12 bits) is sequentially strobed onto a 12-line data bus at 2-μs intervals in the 500 μs between A/D conversions from the memory contained on each amplifier. This provides a data rate of 500 K 12-bit words per second which must be stored continuously for intervals up to 60 minutes for a total of 1.8 M words of storage.

This large data storage problem is accomplished by a Sangamo Sabre IV high-density recorder (HDR) with a 12-parallel-bit storage format. The data are stored at a tape speed of 30 inches per second on 1" wide × 9200 foot 14" reels of Ampex 799 HDR tape and played back at 1-7/8 inches/sec. for a data-speed reduction of 16.

At the slower speed, the effective data transfer rate is 31.25 K-words/sec which makes continuous data storage on conventional disks feasible via direct-memory-access digital input ports and doubly-buffered storage arrays. The computer system utilized to obtain and analyze the data is a Digital Equipment Corporation PDP-11/34 with 2 RL02 10 Mbyte disk drives, DR11W DMA digital interface and a Lexidata color display system.

Data are transferred from regions of interest in the continuously recorded HDR format in sections comprising 5-seconds of real time. The bipolar electrograms obtained are displayed to the operator together with the activation times calculated by the computer. The operator has the option to modify any activation point at this time. The computer next generates the activation map of the regions of myocardium studied in operator-chosen display formats such as epicardial activation alone, transmural activation over a region, etc.

We feel that the inherent strengths of this system such as sampling-frequency flexibility, digital transmission and storage, and flexible data-display format, will provide a powerful capability for the work concerned with delineation of the basic mechanisms of dysrhythmias and the influences of multiple interventions.

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

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Support: AM 20579
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This project is designed to define the kinetics of positron-emitting, radioisotopically labelled tracers that are useful for characterizing myocardial perfusion and metabolism noninvasively. Studies are conducted in isolated rabbit hearts (perfused with a solution containing washed sheep erythrocytes suspended in a modified Krebs-Henseleit buffer) permitting control of the factors that can modify myocardial perfusion and metabolism. Studies are also conducted in anesthetized, opened-chest dogs prior to implementation of approaches of proven value in studies using positron-emission tomography.

The development of accurate, quantitative, noninvasive measurements of myocardial metabolism and perfusion is dependent on thorough characterization of the factors that can influence tracer kinetics. Since fatty acid is the major fuel for the myocardium under normal circumstances, we currently utilize ^{11}C-palmitate to estimate myocardial metabolism. In addition to the external detection of myocardial time-activity curves via coincidence detection of the emitted gamma photons (with analog data fed to the Isolated Probe Data Acquisition System), we measure a number of myocardial and metabolic functions (such as left ventricular pressure, arterial-venous differences of fatty acid and oxygen) simultaneously. Thus, washout curves of ^{11}C-palmitate can be analyzed in a quantitative manner and correlated with myocardial work and substrate utilization. ^{68}Ga-transferrin is employed to estimate the kinetics of vascular transit. By correcting the myocardial time-activity curve after a bolus injection of ^{11}C-palmitate for vascular transit, we have obtained a single monoexponential decay function. By invasive analysis, we have determined that by 7 minutes after a bolus injection of ^{11}C-palmitate, greater than 70% of tracer is trapped in a slowly changing triglyceride fraction. Back-extrapolation of the resultant nonexponential function to the time of peak counts in 32 perfused hearts gave an estimate of extraction fraction which correlated closely (r=.93) with chemically measured arterial-venous extraction fraction.[1] This relationship is maintained even when work is altered by diminishing perfusate flow. Thus, external detection of myocardial time-activity curves gives quantitative information about myocardial substrate utilization.

Of great concern in the noninvasive detection of metabolism is the effect of the relationship between myocardial metabolism and blood flow. To determine whether myocardium can extract a higher proportion of delivered substrate at diminished flow rates, we developed an isolated heart preparation in which flow could be diminished, but in which myocardial work (and therefore substrate utilization) could be maintained constant. In 11 hearts subjected to high work, and 11 subjected to low work (adjusted by alteration of heart rate and left ventricular end-diastolic pressure), when myocardial perfusion was diminished while myocardial work remained constant, hearts extracted increasing proportions of substrate (oxygen, fatty acid, glucose) from the perfusate. This relationship held until the heart mechanically decompensated (that is, could no longer maintain increased workloads with further diminuation of flow). This decompensation occurred despite levels of substrate in the perfusate which exceed the theoretically maximal possible extraction. The results of these studies can be extrapolated to the intact heart (in which, when flow is diminished, work is also affected) to indicate that diminished extraction of palmitate by ischemic myocardium represents diminished metabolic utilization of substrate, and not simply diminished delivery of tracer.[2-4]

To determine factors that influence palmitate washout from ischemic areas in the intact heart, opened-chest dogs were studied in which the left anterior descending coronary artery was perfused via an extracorporeal circuit so that flow rate could be controlled exactly. To determine myocardial time-activity curves resulting from administration of tracer directly into the coronary artery, a probe was designed that detected beta-radiation rather than gamma radiation. The use of this probe permits precise definition of the regional washout rates from selected sub-epicardial regions free from influence of radioactivity emanating from vascular or extra-cardiac sources. Perfusion of the coronary bed with venous blood at normal flow rates produces a relative hypoxia. Under these circumstances, myocardial washout of ^{11}C-palmitate was diminished by greater than 70%, indicating decreased utilization of fatty acid by the hypoxic heart, detectable externally. When the vascular bed was perfused with arterial blood at diminished flow rates (simulating ischemia), time-activity curves resulted in a similar diminution of ^{11}C-radioactivity washout from the myocardium. The results of these studies indicate that diminished clearance of tracer from ischemic segments results from diminished fatty acid metabolism rather than simply diminished delivery and washout of tracer.

Since alterations in myocardial perfusion play an important role in the etiology of cardiac disease, we are currently pursuing methods to quantify myocardial perfusion noninvasively. In a previous study, we demonstrated that although initial distribution of ^{201}Tl (clinically the most commonly used tracer to estimate myocardial perfusion) is related to flow, the extraction and clearance of this tracer is dependent on flow and myocardial oxygenation. To obviate the additional difficulties in quantifying myocardial perfusion with such conventional single-photon radionuclides, studies were undertaken and completed during the past year to examine the use of the positron-radionuclides ^{11}C-butanol and

$H_2{}^{15}O$ as flow tracers. Both tracers are freely diffusible in myocardial tissues, and have tissue:blood partition coefficients of nearly unity. Correlation between tissue quantities of these tracers (determined by well counting) and radioactive microspheres resulted in correlation coefficients of greater than .98. Studies are now in progress to evaluate the suitability of $H_2{}^{15}O$ (since it is simple to produce and permits rapid, sequential evaluation of perfusion) for use with positron-emission tomography.

In addition to completing studies characterizing the fate of ^{11}C-palmitate in isolated perfused hearts with altered levels of substrate, we are currently evaluating externally detectable alterations in the utilization of fatty acids in hearts from rabbits subjected to alcohol,[9] and in hearts from rabbits rendered diabetic by administration of alloxan. Characterization of alterations in palmitate tracer kinetics in hearts from animals with either alcohol or diabetes-induced heart muscle disease may enable the early diagnosis of patients who are developing cardiomyopathies, and may also permit evaluation of the response of the myocardium to therapeutic intervention.

A new project which has been started in the past year in isolated hearts to try to evaluate noninvasively the number of cardiac adrenoreceptors. It has been established that alpha- and beta-adrenoreceptor number and binding affinities may change in a number of cardiac disease states such as ischemia and congestive heart failure. Using the ^{125}I-hydroxybenzylpindolol, we have demonstrated ligand binding to beta-adrenoreceptors, detected externally. Although there is some nonspecific binding, pharmacologic studies have demonstrated that this tracer can be competitively displaced from the adrenoreceptor with both adrenergic antagonists and agonists.[10] Studies are currently underway to determine whether increased numbers of receptors are quantifiable noninvasively in hearts from rabbits subjected to administration of thyroid hormone or in hearts from rabbits in which congestive heart failure is induced by aortic banding. It is anticipated that if these studies demonstrate that receptor number and binding affinities can be detected noninvasively, synthesis of receptor ligands with positron-emitting radiotracers may make the clinical identification of altered receptor numbers possible. Such identification would permit evaluation of the role of alterations in adrenoreceptors in a variety of cardiac diseases, and permit evaluation of the efficacy of pharmacologic therapy.

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A-11. Noninvasive Localization of Electrical Activity in the Heart

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Support: RR 00396
RR 01380
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This project was undertaken to determine the limitations in finding the origin of cardiac electrical activity from measurements made solely on the body surface. The surface distribution of electrocardiographic potentials contains information which can be used to estimate the geometric center of all segments of the heart which may be electrically active at any given instant during the cardiac cycle. If this center of electrical activity is calculated at instants during which only a single, small region of cardiac tissue is depolarizing or repolarizing, then the electrical center should be within and thus locate that small region. Previously the center of electrical activity within the heart was calculated instant-by-instant over the cardiac cycle in one subject.[1] The electrical center was located and moved as expected within the X-ray silhouette of the heart. The electrical-center method of localizing activity, however, was not validated, i.e., it was not used to estimate the location of known depolarization origins in the heart.

In recent years new techniques for understanding and controlling arrhythmias have been introduced which employ cardiac-catheter electrodes to pace the heart. By appropriate placement of electrodes and with proper sequencing of stimuli to these electrodes, certain aspects of the arrhythmias, as seen by both internal and external electrodes can be duplicated. Regions of myocardium involved in the arrhythmias can be inferred from these studies. Because the pacing site is known and can be varied in these studies, these invasive studies will serve as the basis for assessing the accuracy of the electrical-center method for noninvasively finding origins of cardiac activity. The location of pacing sites will be estimated from surface measurements alone for comparison to their actual positions.

Calculation of the electric center requires measuring torso geometry and mapping surface potentials. If the body is modelled as a torso-shaped volume conductor and cardiac sources are represented by a cardiac equivalent generator, then results from potential theory can be applied to find the behavior of that generator in a given torso. The temporal variation of cardiac activity is found by forcing the equivalent generator to match surface potentials, instant by instant, on a least-squares-error basis. The electrical center is that location at which a dipole equivalent generator best matches surface potentials. It is hoped that the electric-center calculation will prove to be reliable and accurate enough to meaningfully estimate the location of pacemaker sites. If it can find the origin

of depolarizations, then perhaps it can be used to diagnose certain cardiac pathologies and to help elucidate mechanisms for cardiac arrhythmias.

The first phase of this project includes the implementation of software to determine the lead field of a homogeneous, human torso for sources in the heart. The lead field tells how a given source in the heart contributes to the electrocardiogram at each point on the torso surface. The lead field calculation requires inversion of a solid angle matrix containing N^2 elements, where N is the number of triangular elements which comprise the torso model. Typically a torso model needs 1000 to 1500 elements. About one half of the software for calculating the lead field can now be run on either a TI980 or on a PDP 11/34 computer. All routines are written in Fortran.

Torso geometry and surface electrocardiograms will be measured in the second phase of this project. About 400 points on the surface are required to represent the torso shape. The torso of each subject in the initial study must be measured. About 200 electrocardiograms measured from sites distributed over the torso surface must be collected for each paced origin in a given subject. ECG's will be collected using a microprocessor-based cart developed at the Biomedical Computer Laboratory. This cart must find adequate signal quality in all 8 leads of a simultaneously acquired set before the set is accepted (PR 17, A-11). In the third phase of this project a multipole cardiac equivalent generator will be calculated for each surface distribution recorded on each subject. The electric center will then be determined from the multipole generator. The electrical-center estimates will be compared to the coordinates of the actual pacing sites to assess the accuracy of the estimates. If the electric center proves to be useful, then a fourth phase will be undertaken. The electric center of naturally occurring normal and ectopic depolarizations will be calculated and compared to positions inferred from catheter studies. Finally, ways to significantly reduce data reduction will be sought. For example, it may be possible to match a subject's torso to one already analyzed rather than make detailed measurements for each new subject.

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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 analysis 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), and 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 the 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 regiment 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 adjuctive 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, 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 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 4,022 patients admitted to the Coronary Care Unit. During that period of 1,922 patients (47%) have been screened for participation in the MILIS protocol. One hundred and seventy-six 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, 1981 through February 28, 1982, forty-two patients were randomized. Of these, 46% received therapy within 8 hours of the onset of symptoms. Eight 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 three 90-minute studies 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. Three additional studies were missed at 72 hours and two patients died prior to the 72-hour study. In two of these instances patients refused and in another a patient was deemed too ill by the Clinical Unit Director and 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, 1981 and February 28, 1982 all follow-up activities were performed in accordance with the MILIS protocol. The activities included 32 three-month follow-up visits, 57 six-month follow-up visits and 108 contacts for subsequent health status forms. Ninety-eight percent of all patients contacts were made. However, 9 of 407 testing procedures were not performed due to the patients' health and to patient refusals. Overall, 94.2% of all end-point data required during the follow-up interval by the protocol were obtained and forwarded to the appropriate Core facilities.

On the recommendation of the MILIS Data and Policy Monitoring Board, the collection of 3- and 6-month Holter recordings was discontinued in early 1982. The in-hospital recordings continue. The extensive database of long-term ECG-recording analyses was combined with that of the MPIP study (A-15) to test a stochastic model of the occurrences of dysrhythmias (A-17).

A-13. Clinical Trials of Nifedipine in Cardioplegia

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Support: RR 00396
RR 01380
HL 17646
HL 24394

Nifedipine, a dihydropyridine light-sensitive compound which is a specific slow-channel blocking agent has been used in a randomized trial at Barnes Hospital in hyperkalemic crystalloid cardioplegia for the past two years. The principal involvement by the Biomedical Computer Laboratory was in the analyses of Holter monitor tapes which were recorded preoperatively and then continuously for the first 72 hours postoperatively, at one week and at 8 weeks after surgery. Tape analysis was performed by the Argus/2H system and reports were returned promptly for clinical use. An analysis of the first 66 patients (26 control, 40 treated) demonstrated that overall there was no initial difference in PVC rate between the two groups prior to operation and that use of the drug caused no change in the rate of PVC development or ablation in the immediate postoperative interval. The principal problem involved in use of Holter monitors in the immediate postoperative interval was the incidence of external pacing required in the Intensive Care Unit setting to optimize cardiac output which consequently made PVC analysis nearly impossible. For this reason, and because after 18 months of study it became apparent that the presence or absence of the drug did not make a difference in the incidence of arrhythmia in the postoperative interval, this component of the study was discontinued.

A-14. Model Development for Cardiac Diastolic Mechanics

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Cardiac diastolic mechanics, i.e., the passive mechanical properties of the left ventricular (LV) muscle and chamber, are less well understood than are the more thoroughly investigated systolic functions. Quantitative measures of diastolic behavior are expected to be more sensitive than many systolic markers, to be important prognostic markers, and to aid in therapeutic (particularly pharmocological) interventions.

Pressure-volume (P-V) expressions describing the behavior of the LV chamber have been the prime measures of diastolic compliance. The form of the P-V relationship has not been determined, although functions of the form $P=a+bc^{CV}$ and $P=ae^{bV}$ have been suggested in publications. We fit human LV P-V data with these two functions along with a third-order polynomial. The exponential function with the constant term provided better fits than the other two functions, and in addition, the exponential constant appears to be a clinically useful index of stiffness.

P-V expressions are inherently a measure of LV chamber rather than muscle properties and are strongly dependent on the LV geometry. As such, they are of limited value in comparing stiffness between different patients. Elastic stiffness, as a function of stress (σ) and strain (ε), provides a measure of muscle properties. A variety of definitions for ε (natural, Lagrangian, etc.) have been used. Stress depends on a number of geometric as well as physiologic assumptions, but is a function of intra- and extra-cavitary pressure, cavity radii (measured or derived), and wall thickness. Pressures are accurately measured in the cardiac catheterization lab using catheter-tip micromanometers. Dimensional data are acquired from single-plane angiographic silouettes, specifically by measuring the area and longest chord of the ventricle and then deriving the other radius as well as the volume.

Fidelity of dimensional data is a major practical problem, especially in computing a σ vs. radius relationship. Stress typically changes by 300% while the radius changes by 10%, necessitating accurate dimensional measurements. Our investigation of a number of curve-fits for the dimensional data (area and chord vs. time) indicated that a fourth-order polynomial provided good smoothing of the raw data without filtering out meaningful information. Using the smoothed data, other radii and volumes are calculable.

Wall thickness is also, under practical limitations, subject to large error. Therefore, it is measured at end diastole and assuming a constant wall mass during the cardiac cycle, calculated for other frames in the cardiac cycle.

Finally, the pressure and dimensional data are combined into ε, σ, and elastic stiffness calculations. Our initial efforts have used natural strain and a thick-walled, prolate ellipsoid model for stress. If σ is a monoexponential function of radius then elastic stiffness ($d\sigma/d\varepsilon$) and the elastic stiffness coefficient are directly calculable. Although this σ vs. radius relation is attractive from a physiologic and mathematical viewpoint, suboptimal fits to the data are limiting the accuracy of our results at this time. We are actively pursuing other models.

A-15. Multicenter Post-Infarction Program

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The purpose of the Multicenter Post-Infarction Program (MPIP) has been previously described in reports, PR 15, A-19, PR 16, A-19, and PR 17, A-15.

Analysis of Holter tapes was completed during the previous year, thus bringing to a close BCL's active participation. The remainder of the work involved completion of the two-year follow-up and data clean-up tasks. Follow-up on the 126 patients enrolled at St. Luke's-East and Jewish Hospital in 1979 and 1980 continues. Periodic telephone interviews ascertain current clinical status and medication profiles. Forms and summaries of each re-hospitalization are completed. In the case of an expiration an additional "Terminal Event" summary and data forms are completed and submitted to the executive review board. Yearly newsletters were mailed to the participating patients and physicians.

The extensive database of long-term ECG-recording analyses was combined with that from the MILIS study (A-12) to test a stochastic model of the occurrences of dysrhythmias (A-17). Further analysis of the collaborative database will continue, primarily by non-BCL personnel.

A-16. The Characterization of Non-Sustained Ventricular Tachycardia

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Support: RR 00396
RR 01380
HL 17646

The mechanisms underlying non-sustained ventricular tachycardia (VT) are poorly understood. To characterize non-sustained VT, defined as four or more premature ventricular complexes (PVC) in a row, we are studying the normal-to-PVC coupling interval, the QT interval, the length of the VT, and the average coupling interval of the initiating PVCs and terminating PVCs of the non-sustained VT. The morphology of non-sustained VT (uniform runs versus polymorphic runs) is also under examination as a possible discriminant of patients prone to sustained VT.

A-17. A Stochastic Model of the Occurrences of Dysrhythmias in Long-Term ECG Recordings

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The most troublesome issue in the use of long-term ECG recordings for quantifying dysrhythmias stems from the very high intra- and inter-patient variability in the frequencies of occurrence of the events of interest. It is common to observe that the standard deviations of mean PVC rates are often of a similar order or magnitude as the mean rates themselves. Accordingly, dramatic event-rate reductions (75% to 95%) are often required to infer therapeutic efficacy in an individual patient. Also, study designs suffer substantial uncertainty due to the difficulty of developing predictive estimates of prevalences of various dysrhythmic manifestations in the target population. The particular issue of concern is what recording protocol (especially recording duration) should be employed to adequately characterize the frequencies of occurrence of dysrhythmias of interest before and after interventions in order to detect differences beyond those expected due to spontaneous variation. To address

these difficulties, we have developed a stochastic model based on the assumption that for an individual patient, the generation of dysrhythmias can be viewed as a Poisson process in the time domain. The model can then be applied to population prevalences by adding the empirical observation that the frequencies of occurrence of most dysrhythmic manifestations show a log-normal distribution.

For an individual with an underlying event rate, ρ, and who is observed for a time period, T, the probability of seeing an observed event rate, r_o, is (assuming a Poisson process):

$$P(r_o|\rho,T)=\frac{\lambda^{X_o}e^{-\lambda}}{X_o!}$$

where $X_o = r_oT$ and $\lambda = \rho T$. More usefully,

$$P(r_o \geq r_{th}|\rho,T)=1-\sum_{X_o=0}^{X_{th}-1}\frac{\lambda^{X_o}e^{-\lambda}}{X_o!}$$

gives the probability of observing an event rate greater than or equal to some threshold rate, r_{th}. For patient populations the probability of observing a particular event rate is simply the product of the probability that r_o will be observed, given ρ, times the probability that ρ will occur, integrated over ρ. Thus

$$P(r_o)=\int_{\rho=0}^{\infty}P(r_o|\rho)\cdot P(\rho)\,d\rho$$

where $P(r_o|\rho)$ is the Poisson distribution considered above and $P(\rho)$ is the log-normal distribution of ρ, i.e.

$$P(\rho)=\frac{\exp\left[-\frac{1}{2}\left(\frac{\ln\rho-\mu}{\sigma}\right)^2\right]}{\sigma\sqrt{2\pi}}$$

where μ is the mean and σ is the standard deviation of $\ln \rho$.

The adequacy of the model was assessed by comparing predicted prevalences of various dysrhythmic events as a function of recording duration, based on the results of 2,366 24-hour recordings analyzed for the Multicenter Investigation of the Limitation of Infarct Size (MILIS, PR 17, A-12) and Multicenter Post Infarction Program (MPIP; PR 17, A-15) studies, against comparable observations from two published studies[1,2] of unrelated but similar patient populations. The results are shown in Figure 1. The model and published values are gratifyingly similar, especially considering that the relatively small positional differences are compatible with expected differences in the patient populations.

Preliminary results of this work were presented at the 16th annual AAMI meeting last year[3] and a more complete exposition is in preparation for an NHLBI Workshop on Pharmacology of Antiarrhythmic Therapy to be held in September, 1982.

1. J. T. Bigger, L. M. Rolnitzky, E. B. Leahey, and J. D. LaPook, "Duration of Recording; Activity Protocol," in Ambulatory Electrocardiographic Recording, N. Wenger, M. Mock, and I. Rinqvist, eds., Yearbook Medical Publishers, Chicago, pp. 87-102, 1981.

2. S. Thanavaro, R. E. Kleiger, B. R. Hieb, R. J. Krone, V. R. deMello, and G. C. Oliver, "Effect of Electrocardiographic Recording Duration on Ventricular Dysrhythmia Detection after Myocardial Infarction," Circulation, vol. 62, pp. 262-265, 1980.

3. L. J. Thomas, Jr., J. P. Miller, K. W. Clark, and G. C. Oliver, "Perspectives on Information Extraction from Ambulatory Recordings," Proceedings of the 16th Annual Meeting of the Association for the Advancement of Medical Instrumentation, Arlington, Virginia, p. 98, 1981.

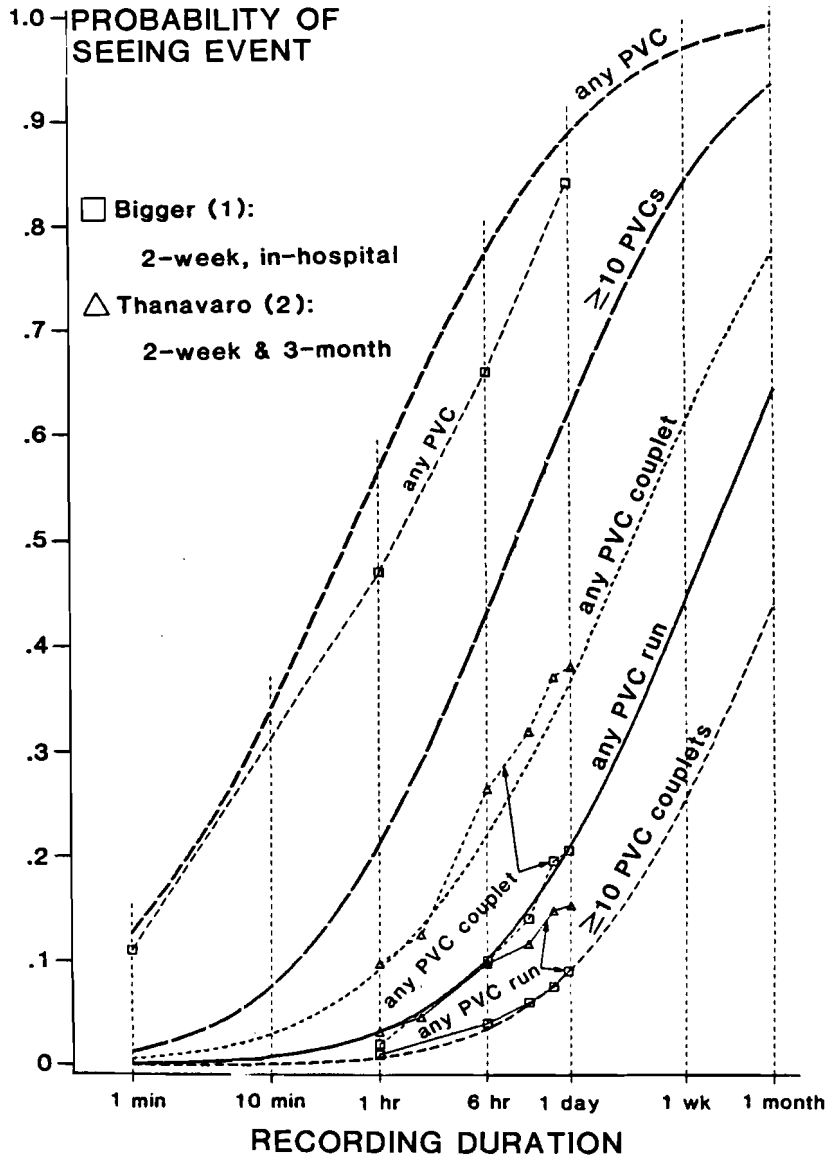

Figure 1. Probability of seeing various VEA manifestations on ECG recordings as a function of recording duration (on a log scale). The continuous curves are derived from the model described in the text (Poisson process plus log-normal distribution of prevalences). Corresponding data from two published reports are plotted for comparison.

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. In a collaborative effort with Cardiology and the Department of Physics, work has continued on methods of tissue characterization via ultrasound. Quantitative images based on ultrasonic tissue properties have been made at the BCL for several years using transmitted ultrasound with a multiple-frequency tomographic reconstruction system (B-1). This system was used this year to obtain detailed measurements of anisotropy of attenuation in canine heart and liver (B-4), and to initiate studies of anisotropy in backscatter (B-5) and of anisotropy in velocity (B-6). Further tests were made with software designed to evaluate strategies for ultrasonic transmission and tomographic reconstruction (B-2). A simulation of transmission and reception using a single linear phased array is being extended to study errors in measurements of regional attenuation via reflected ultrasound (B-3). Beamforming methods for use with signals received from an inhomogeneous medium with a transducer array have been identified (B-7).

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 (B-8) have been implemented with special-purpose hardware (B-9). The speeds achieved thereby, together with the progress made in developing appropriate displays of the computed results (B-10), have inspired plans for integrated-circuit implementations (B-11) and 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-12 to B-15). 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. PETT VI became operational during the summer of 1980 and employs fast detectors and an entirely circular motion for rapid data acquisition. Further experimental and clinical studies with this system occurred over this past year (B-16). One of the most exciting recent developments 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 of tomography systems that utilize this new information continued, and the software and hardware needed to realize the predicted benefits were developed (B-17 to B-27); the new system is called SUPER PETT-I.

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

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Support: RR 00396

Progress is being made on the integration of an LSI 11/23 microcomputer into the existing data acquisition and analysis system (PR 17, B-1). The LSI 11/23 offers three important advantages over the PC-1200 processor which is presently the heart of the scanner. First, the LSI 11/23 is much more reliable and more easily maintained than the PC-1200 which is no longer in production. Second, it contains four times the memory of the PC-1200, so that software overlays can be eliminated. Third, the time for data analysis required for the analysis and reconstruction of attenuation and time-of-flight based images will be greatly reduced with the use of the FPS 100E array processor associated with the LSI 11/23.

Most acquisition system hardware including the Biomation 8100 waveform recorder and stepper motors which rotate and translate the transducers have been interfaced to the LSI 11/23 via an IEEE 488 bus. Driver software is being developed for the Biomation recorder (E-6), the stepper motors, and other hardware of the scanning system. Display systems including a Versatec plotter and Digivision, a locally developed raster-scan imaging system (PR 15, G-9; PR 16, G-5), have not yet been transferred to the LSI 11/23 system.

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

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Support: RR 00396

In previous reports we have identified and investigated a number of potential sources of error in tomographic reconstructions of the ultrasonic attenuation in soft tissue. Computer simulation offers the potential for segregating and characterizing the nature of each of these sources of error and for evaluating strategies to achieve improved accuracy. The geometrical ray tracing approach, which is described in detail in the previous progress report (PR 17, B-2) provides the basis for investigations of this sort.

We have made use of a computer model based on geometrical acoustics to simulate the generation, propagation, and detection of ultrasound. In this model, the transmitted beam was modeled as a superposition of 100 rays each of which was characterized by a frequency dependent amplitude, phase, and trajectory in order to achieve a Bessel function-like beam. Soft tissue was modeled as a superposition of regions each of which was characterized by a velocity, mass density, and frequency-dependent ultrasonic attenuation. Detection by both phase-sensitive (piezoelectric) and phase-insensitive (e.g., acoustoelectric) receivers was investigated.

Results of these computer simulations demonstrate the advantages of the following approach:

1) Use a phase-insensitive receiver (to eliminate phase-cancellation errors) of relatively large aperture and positioned relatively close to the tissue (to capture a substantial fraction of the refracted beam),

2) Reconstruct the slope of the attenuation as a function of frequency (to reduce refraction and reflection effects), and

3) Compensate for the frequency dependence of the width of the insonifying ultrasonic beam prior to calculating the slope.

B-3. Estimation of Ultrasonic Attenuation with Linear Phased Arrays

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This work is an extension of a study of the resolution of linear, phased arrays used for ultrasonic imaging (PR 17, B-5). In that simulation we included the effects of array geometry, form of the excitation (assuming a unity transfer function for the transducer), focus mode, and steering angle on the performance of a transducer array. The array was composed of rectangular elements. The dimension of the elements and the number of elements in the array was variable. We simulated the transmission, scattering, and reception of ultrasound in a homogeneous medium. All scatterers were point targets. We determined resolution by varying the spacing of two point targets until the received signals showed two clearly separable peaks as the targets were scanned.

The objective of this study is to determine the major errors in estimating regional attenuation introduced by a transducer array. To meet this objective we have begun to extend the linear-array performance model described above, in two ways. First, we greatly increased the number of scatters, so that we can simulate a cluster of scatterers which might be

found in tissue. This addition allows us to study the effects of the beam profile on attenuation measurement. Second, we have begun to develop a phenomenological model for the transfer function of the transducer, i.e., the relation between the electrical excitation and the motion of the face of the transducer.

Beam patterns vary throughout the field of an array due to the diffraction of that array. To study the effects of the diffraction pattern on the estimate of attenuation, we are presently adding to the model the capability of reflecting ultrasound from both uniform and random distributions of scatterers. These clusters have a spatial extent which is great enough to encompass most of the energy in a focused beam. Reflections from a given cluster will vary, depending on the location of the cluster, because of differences in the constructive and destructive interference of the signals from the scatterers within the cluster. Thus changes in the beam due to the diffraction of the array will give rise to different reflected signals from the same cluster placed in different regions of the medium, even if the medium is lossless. The effect of the differences in reflections from different locations will give rise to an apparent attenuation in a lossless medium. We expect to be able to quantify the relation between this apparent attenuation and the resolution of the array. This simulation, which has been carried out on a TI 980 minicomputer, is very demanding computationally. We intend to pursue the use of the FPS 100E array processor which will be acquired in the fall of 1982 to significantly reduce the time spent in calculation.

The transducer also introduces effects which can lead to errors in estimating attenuation because of cross-talk among elements of an array and because the transfer function from electrical to acoustic signals and vice versa is not unity. To characterize the transfer function of a given transducer we propose to model each element as a collection of facets or sub-elements. The relation between each sub-element and the pressure field it generates is found by the impulse response method employed in the existing model to describe the entire element (PR 17, B-5). We plan to measure the pressure patterns generated by single elements or small groups of elements with a hydrophone in a water tank. We hope to be able to infer the motion of the facets or sub-elements on a least-squares-error basis. If the motion of the transducer face, including effects of cross-talk, can be found, then the transfer function can be calculated because the electrical stimulus is known.

If this study is successful, it will establish a limit on the accuracy with which a given array can measure regional attenuation in a homogeneous medium. The next step in simulating the actual situation encountered in medical ultrasonic imaging will be to include the effects of tissue, which is both dispersive and inhomogeneous (B-7).

B-4. Anisotropy of Ultrasonic Attenuation in Soft Tissues

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Several authors, dating as far back as Hueter[1] and as recent as Nassiri et al,[2] have reported that differences in ultrasonic attenuation were noted when ultrasound traveled parallel to as opposed to perpendicular to the fibers of muscle tissue. Previously we examined the implications of anisotropy for computed transmission tomography (PR 17, B-3). During the past year we have begun to explore the use of anisotropy as a tissue signature.[3]

The objective is to determine the magnitude and angular dependence, i.e. the degree of anisotropy, of the ultrasonic attenuation in soft tissues. Here we report on preliminary studies performed on gelatin phantoms and specimens of excised canine liver and myocardium.

Figure 1 shows a small volume element of a specimen. We say that this element exhibits anisotropy if the measured attenuation varies systematically with the direction of propagation of ultrasound relative to some intrinsic direction, referred to as the anisotropy axis. As a reference when reporting the angle of propagation, an anisotropy axis is defined as the direction along which the maximum attenuation is measured. Studies from other laboratories, confirmed by this work, have reported that the largest attenuation in muscle is measured when sound propagates parallel to the fibers of the tissue, suggesting a physical origin for the anisotropy axis.

Figure 2 schematically illustrates the measurement of attenuation scan lines in a transmission experiment. The ultrasound travels from transmitter to receiver through an attenuating object. The relative orientations of the transmitter-receiver pair and the object are changed and the variation of the total attenuation noted. This variation with angle may arise from several sources. Extrinsic effects arising from such factors as reflection and refraction at edges or phase distortions of the acoustic wavefronts which lead to phase-cancellation artifacts when measured with phase sensitive receivers, can cause an apparent anisotropy. The goal of the present study was to segregate intrinsic, or true, anisotropy from these extrinsic effects which are a potential source of error.

Our approach was to measure the attenuation as a function of position in cylindrical specimens of tissue at multiple angles, and to segregate intrinsic anisotropy from extrinsic effects arising from phase cancellation, reflection, and refraction.

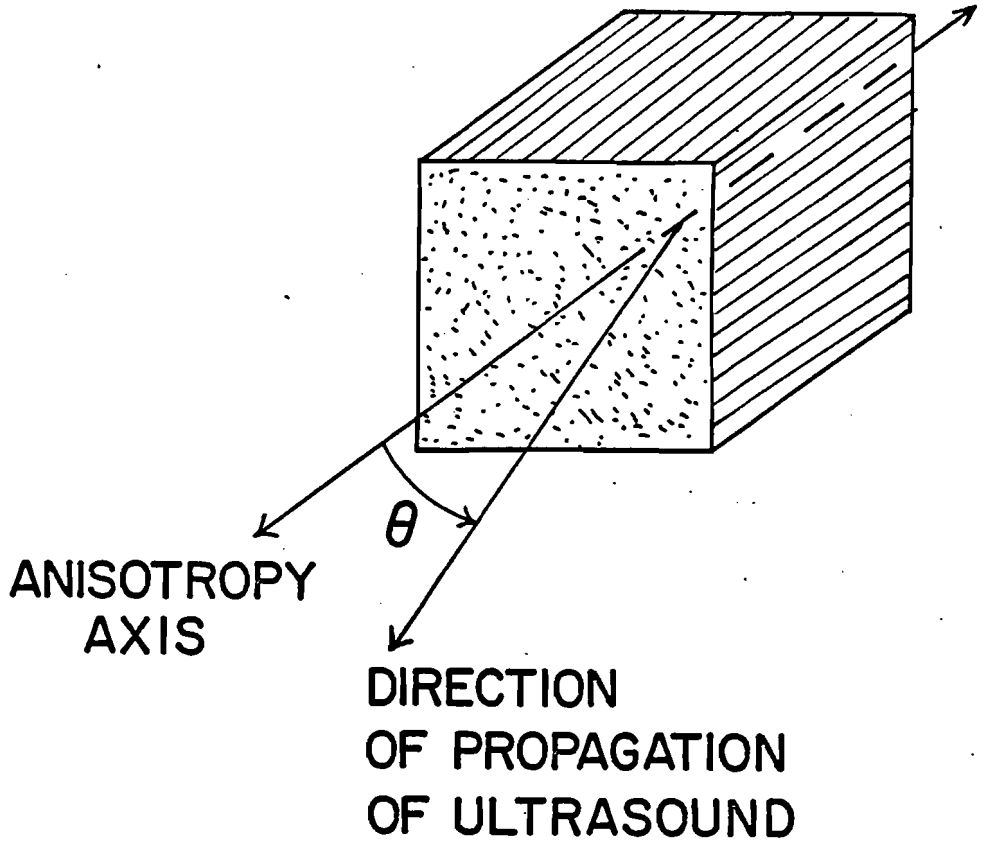

Figure 1. A small volume element of an anisotropically attenuating object is illustrated. The direction of maximum attenuation is defined as the anisotropy axis.

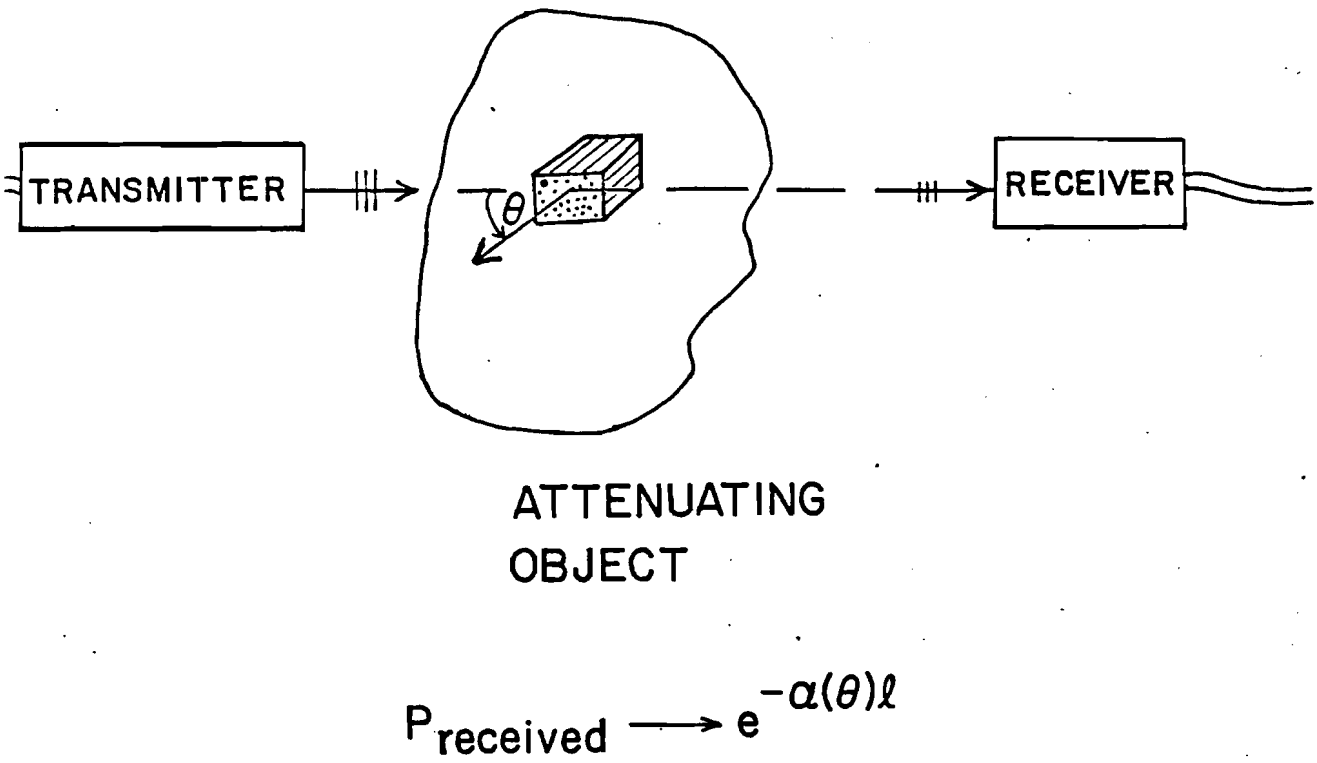

Figure 2. A schematic representation of the measurement of attenuation anisotropy using a translate-rotate tomographic apparatus.

The ultrasonic methods used were as follows: attenuation scan lines were measured as a function of frequency over the range 2 to 7 MHz, in a translate-rotate tomographic system (B-1). A phase-insensitive acoustoelectric receiver was used to eliminate phase-cancellation errors. The slope of the attenuation coefficient as a function of frequency was calculated to minimize the extrinsic effects of reflection losses and refraction errors. The zeroth moment (average slope) of the scan line obtained at each angle was computed as an index of the total attenuation occurring at that angle.

Figure 3 illustrates the use of the zeroth moment of a scan line (M_0) as an index of total attenuation. If an ideal cylinder with a uniform but anisotropic attenuation is scanned at different angles, we obtain scan lines such as those shown. In this case we have simulated a 2:1 anisotropy, that is, the attenuation at 0 degrees is twice that at 90 degrees. When we calculate the zeroth moment of these scan lines, we see that the moment is the cross-sectional area times the attenuation at that angle. Thus, knowing the attenuation at one angle and the moment at all angles allows us to calculate the attenuation at all other angles.

Four-microsecond tone bursts with center frequencies ranging from 2 to 7 MHz were applied to a commercial, broadband, piezoelectric transducer, and were received with a phase-insensitive acoustoelectric transducer, made in our laboratory.[4] Received signal strength was normalized to the signal received when no tissue was present in a substitution technique. Scan lines, or projections, were taken at 61 angles distributed through 360 degrees. Frequency, transmitter gain, and transducer position were all computer controlled.

Four adult mongrel dogs were sacrificed and the liver and heart were excised. Cylindrical specimens were prepared from each organ, three from each liver and one from each heart. The liver cylinders were cut so that the axes of the cylinders were mutually orthogonal, and the heart cylinder was obtained from the posterior left ventricular wall between the papillary muscles, with the axis parallel to the long axis of the heart. The heart cylinder thus had the dominant fiber orientation parallel to one diameter, due to the nearly circumferential orientation of the muscle bundles. Specimens were immersed in a degassed, isotonic sodium citrate bath and massaged to expel air. Attenuation scan lines were obtained from several planes of each specimen. Cylinders of graphite-doped gelatin of similar sizes were scanned as controls for extrinsic effects.

Scan-line data were analyzed offline. The scan lines at each frequency were filtered to compensate for the frequency dependence of the transmitted beam. The slope of attenuation as a function of frequency was calculated. The average slope, or zeroth moment, of each scan line was computed as a reliable index of the total attenuation occurring at that angle. These moments were then normalized to the slope measured at particular directions, i.e., at an arbitrary 0 degrees for liver and at the minimum attenuation direction for heart.

Previous reports had indicated that the attenuation was maximum when sound traveled parallel to the fibers of muscle tissue. Some attenuation occurs at all angles, so a function which describes the angular dependence must be positive everywhere, and the period of the function must be 180 degrees,

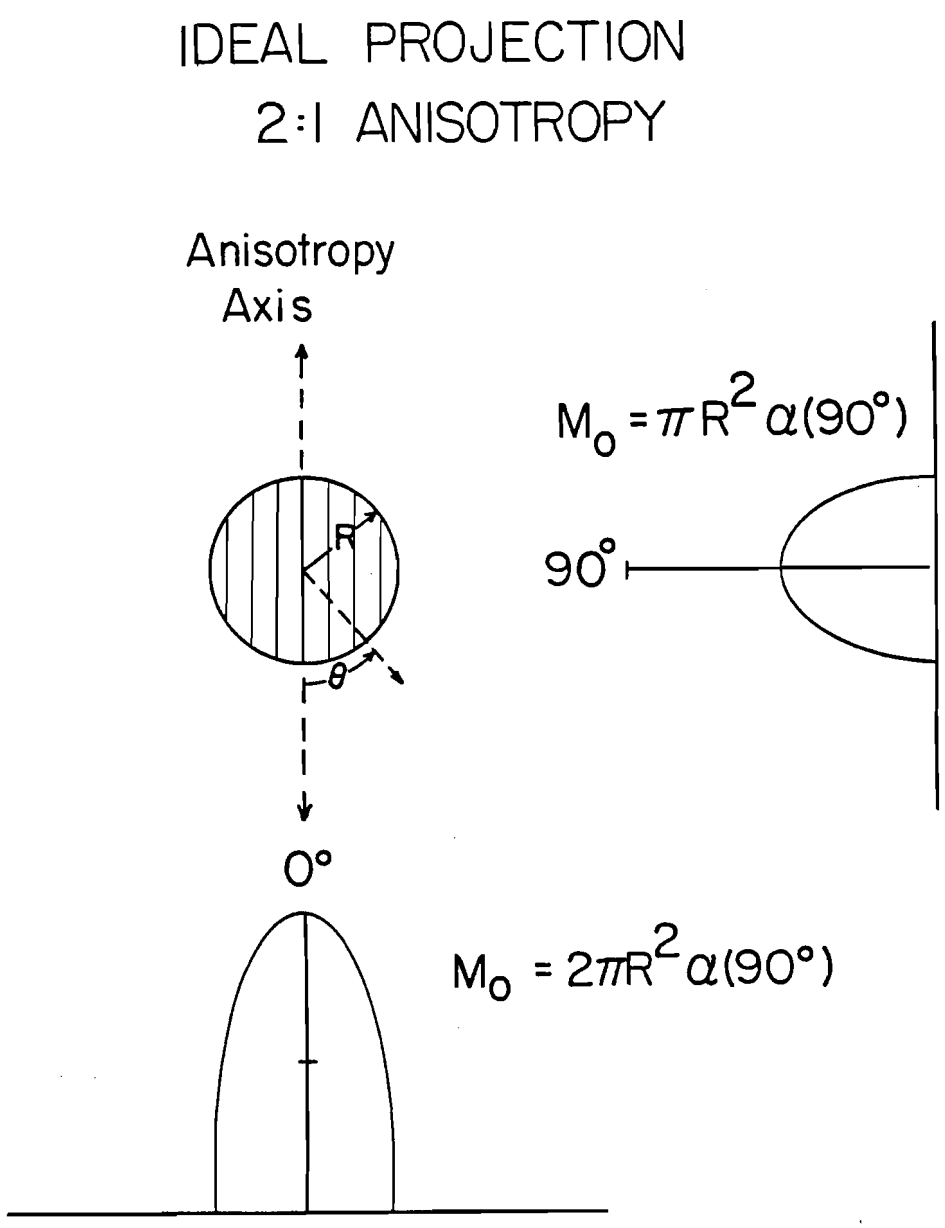

Figure 3. This figure illustrates the use of the zeroth moment of a scan line (denoted M_0) as an index of the total attenuation occurring at that angle. M_0 is seen to be the cross-sectional area of the object times the attenuation coefficient at that angle.

because the direction along the fibers (i.e. "up" or "down" the fibers) does not matter, only whether the sound travels parallel or perpendicular to the fibers. From these considerations, a general functional form of $A+B\cos(2\theta)$, where θ is the angle of propagation relative to the fibers, was chosen as the form to which the data would be fit.

Thus, the normalized slopes as a function of angle were fit to the functional form $A+B\cos(2\theta)$, and phase shifted to have zero phase offset. It must be noted that this phase shifting to force alignment will reinforce any periodic variations present, from any cause. The phase-aligned, normalized slopes at each angle were then averaged over all specimens and all animals. These average slopes were fit to a form $A+B\cos(2\theta)$. The magnitude of the anisotropy is reported as a ratio of maximum slope to minimum slope, i.e., as the ratio of $(A+B)/(A-B)$.

Figure 4 shows the results of the experiments on cylinders of laboratory gelatin, which were doped with powdered graphite. We have plotted the normalized slope of the attenuation in $(\text{cm MHz})^{-1}$ as a function of angle of propagation. Data values (boxes) are plotted as mean $\pm$ the standard error of the mean. The solid line is the fit of the data to the form $A+B\cos(2\theta)$. The maximum to minimum ratio is 1.08, indicating the magnitude of the experimental error.

Figure 5 illustrates the results obtained from measurements on 12 specimens from the livers of 4 dogs. Again we plot the slope of attenuation as a function of angle of propagation, and indicate the measured values as boxes and the fit curve as a solid line. Here the ratio of maximum to minimum of the fitted cosine curve is 1.2. However, we note that the root mean squared deviation to this form is the same as the root mean squared deviation to a flat, constant value, indicative of an isotropic tissue.

Figure 6 shows the results of experiments carried out on 11 specimens of heart tissue obtained from 4 dogs. Again we show the slope of attenuation as a function of angle of propagation, with the data as boxes and the fit curve as a solid line. The quality of fit to the cosine curve is high, with the maximum attenuation occurring when the ultrasound travels parallel to the dominant fiber direction and the minimum occurring when the sound travels perpendicular to the dominant fiber direction. The maximum to minimum ratio is 2.2, indicating a large systematic variation of the attenuation with angle.

In summary, our results indicate that anisotropy of the attenuation is a highly significant effect in myocardial tissue which represents a challenge to ultrasonic tissue characterization techniques. We note, however, that anisotropy of the ultrasonic attenuation may prove to be a useful tissue signature.

1. T. F. Hueter, "Messung der ultraschallabsorption in tierischen geweben und ihre abhangigkeit von der frequenz," Naturwissenschaften vol. 35, pp. 285-286, 1948.

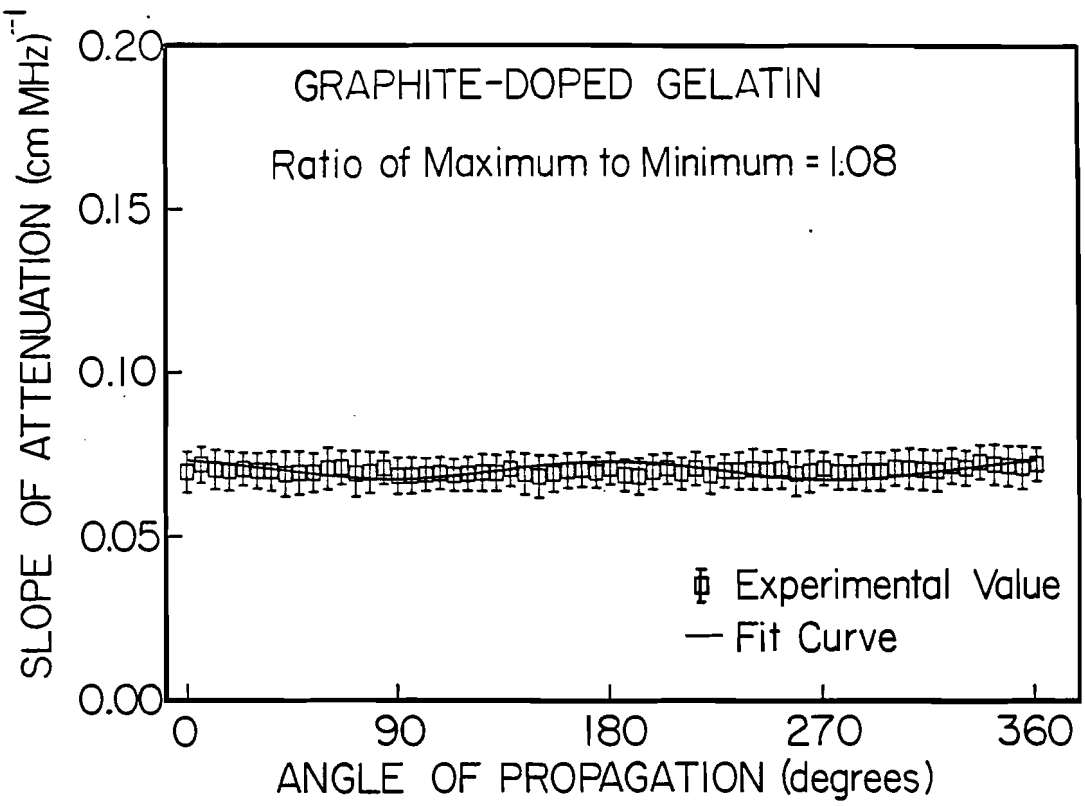

Figure 4. The slope of the attenuation as a function of the angle of propagation through a specimen of graphite-doped laboratory gelatin. The specimen is said to be isotropic due to the lack of dependence of the slope of attenuation on angle.

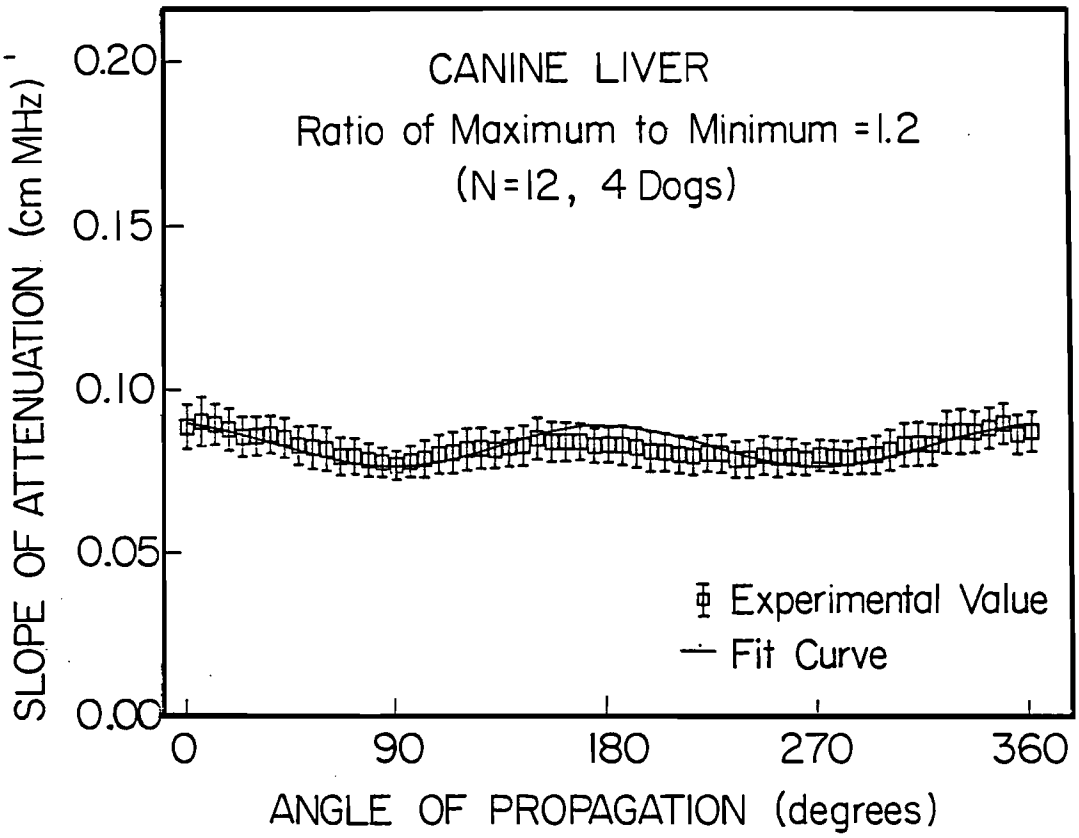

Figure 5. The average slope of attenuation as a function of angle of propagation in canine liver (N=4 animals). The root mean squared deviation relative to the fitted cosine curve shown is the same as the root mean squared deviation to a flat line. Thus, liver is also isotropic.

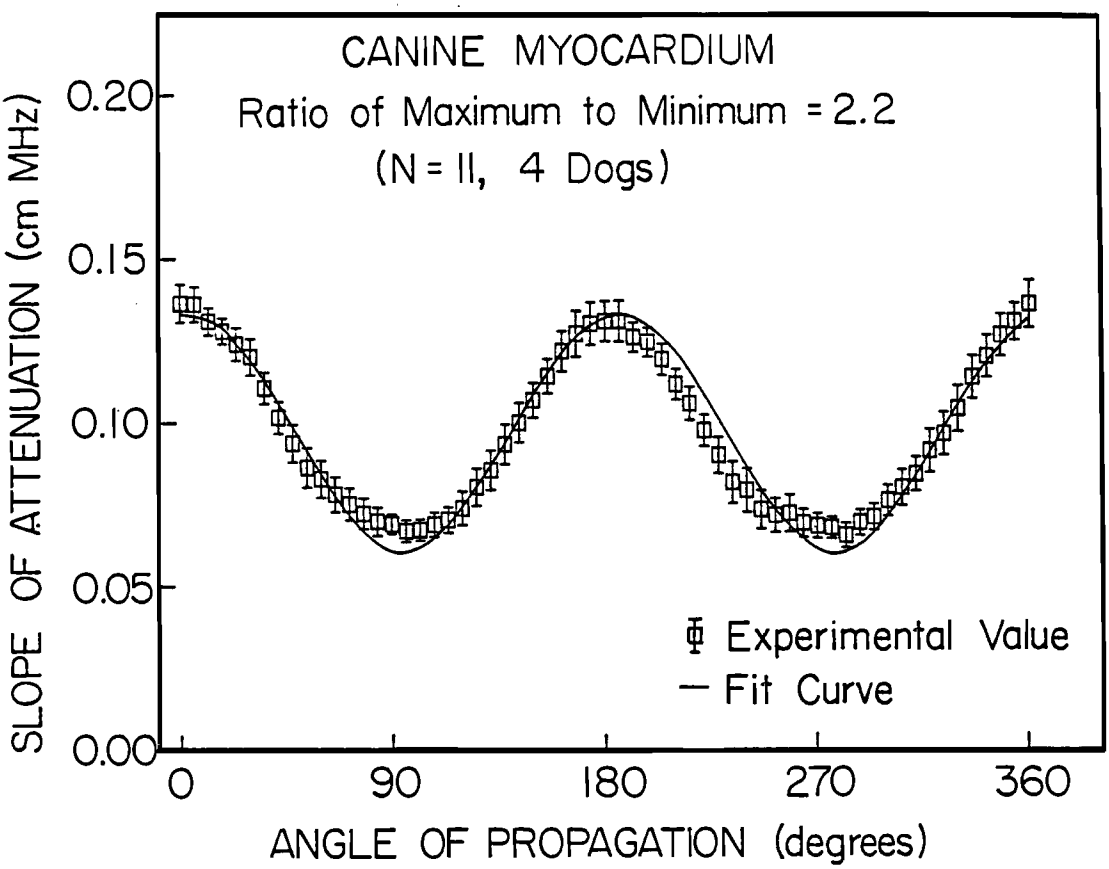

Figure 6. The average slope of attenuation as a function of angle of propagation in canine cardiac muscle (N=4 dogs). The quality of fit to the cosine curve is high, thus cardiac muscle is said to be anisotropic.

2. D. K. Nassiri, D. Nicholas, and C. R. Hill, "Attenuation of Ultrasound in Skeletal Muscle," Ultrasonics, vol. 17, pp. 230-242, September 1979.

3. J. G. Mottley and J. G. Miller, "Anisotropy of Ultrasonic Attenuation in Canine Heart and Liver," Ultrasonic Imaging, vol. 4, p. 180, 1982 (abstract).

4. L. J. Busse, J. G. Miller, D. E. Yuhas, J. W. Mimbs, A. N. Weiss, and B. E. Sobel, "Phase Cancellation Effects: A Source of Attenuation Artifact Eliminated by a CdS Acoustoelectric Receiver," in Ultrasound in Medicine, vol. 3, D. White, ed., Plenum Press, New York, pp. 1519-1535, 1977.

B-5. Anisotropy of Ultrasonic Backscatter in Soft Tissues

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Support: RR 00396
HL 17646

The only report we know of which contains measurements of the dependence of backscatter on the angle of insonification in muscle is the 1953 paper by Wild and Reid.[1] That report only qualitatively describes the differences observed in one specimen of muscle tissue. The objective of this study is to determine the magnitude and angular dependence, i.e., the degree of anisotropy, of the ultrasonic backscatter in soft tissues. Here we report preliminary results obtained from specimens of excised canine liver, myocardium, and skeletal muscle.

Tissue samples were obtained from several adult mongrel dogs. The dogs were sacrificed and the liver, heart, and a portion of the muscle of the hind leg excised. Cylindrical specimens were prepared from each tissue. Specimens were immersed in a degassed, isotonic saline bath and massaged to expel air. Energy backscattered from a region of tissue in the center of each specimen was measured every 6 degrees through a full 360 degrees (PR 17, B-1; B-1). The measurements spanned the frequency range of 2 to 7 MHz, and were made using an analog spectrum analyzer under the control of a microprocessor. Calibration spectra were measured from a stainless steel plate placed at the same distance as was used for the tissue. After recording the above data, the tissue spectra at each angle were normalized to the calibration spectra. Then the frequency average, or integrated, backscatter was computed as an index of the backscatter strength at that angle.

The choice of the general functional form $A+B\cos(2\theta)$ for the angular dependence of backscatter was made based on the same arguments as for the attenuation in section B-4. The values of the integrated backscatter were fit as a function of angle to the functional form $A+B\cos(2\theta)$, and phase shifted to have zero phase offset. For each tissue, the phase-aligned integrated

backscatter at each angle was then averaged over all specimens and all animals. The average backscatter was also fit to a form $A+B\cos(2\theta)$. The magnitude of the anisotropy is reported as the peak-to-peak excursion about the central value, i.e., 2B.

Figure 1 illustrates the results obtained from measurements on 9 specimens from the livers of 4 dogs. We plot the integrated backscatter as a function of angle of propagation, and indicate the measured values as boxes and the fit curve as a solid line. Here the difference between the maximum and the minimum of the fitted cosine curve is 6 dB. We note that the fit to the cosine curve is poor, indicating the absence of a strong, linearly directed anisotropy.

Figure 2 shows the results of experiments carried out on 7 specimens of heart tissue obtained from 4 dogs. Again we show the integrated backscatter as a function of angle of propagation, with the data as boxes and the fit curve as a solid line. The quality of fit to the cosine curve is-high, with the maximum backscatter occurring when the sound propagates perpendicular to the muscle fibers, and the minimum occurring when the sound travels parallel to the dominant fiber direction. The difference between the maximum and the minimum is 14 dB, indicating a moderate systematic variation of the backscatter with angle.

Figure 3 shows the results of experiments carried out on four specimens of canine skeletal muscle from two dogs. The maximum to minimum difference is 22 dB, indicating a very substantial variation of the backscatter with angle.

In summary, our preliminary results suggest that anisotropy of the backscatter is a highly significant effect in myocardial and skeletal muscle which represents a challenge to ultrasonic tissue characterization techniques. On the other hand, anisotropy of the ultrasonic backscatter may prove to be a useful tissue signature.

1. J. J. Wild and John M. Reid, "The Effects of Biological Tissues on 15-mc Pulsed Ultrasound," Journal of the Acoustical Society of America, vol. 25, no. 2, pp. 270-280, March 1953.

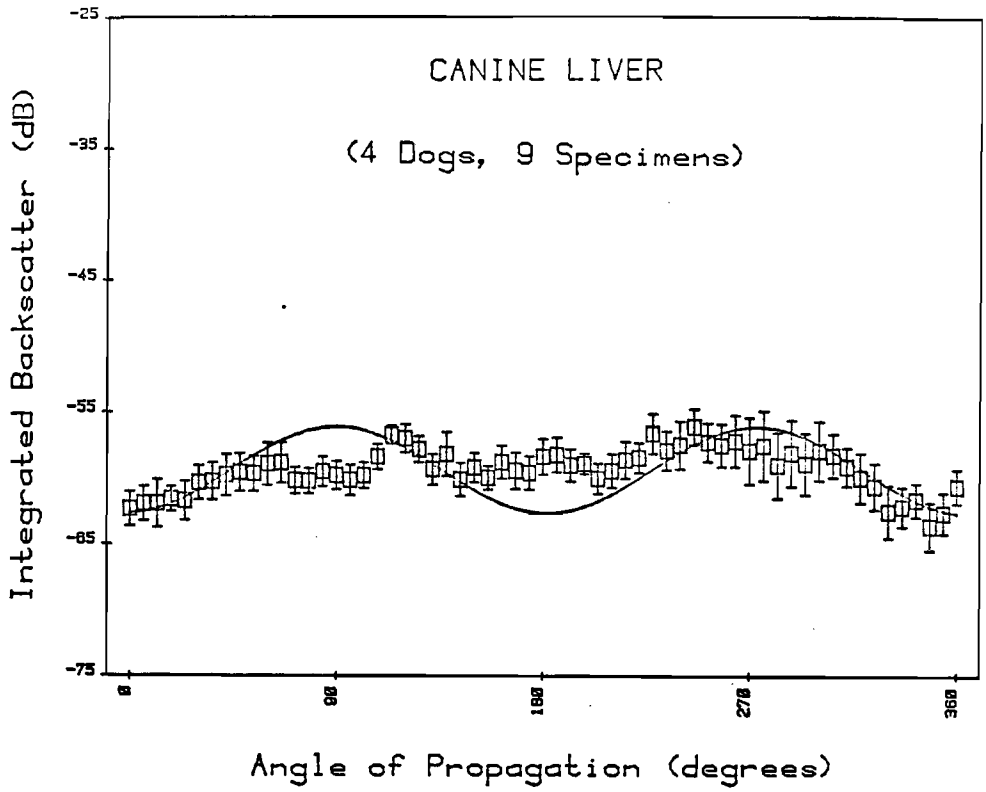

Figure 1. The integrated backscatter of canine liver as a function of angle of propagation. The maximum to minimum difference is 6dB.

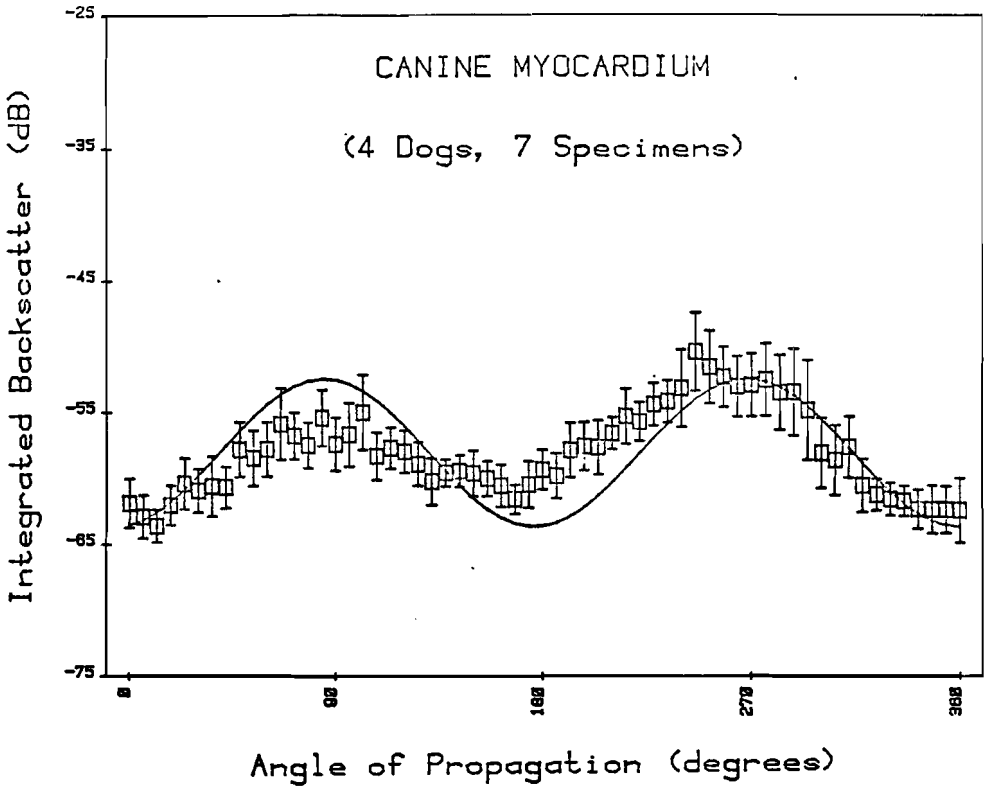

Figure 2. The integrated backscatter of canine myocardium as a function of angle of propagation. The maximum to minimum difference is 14 dB.

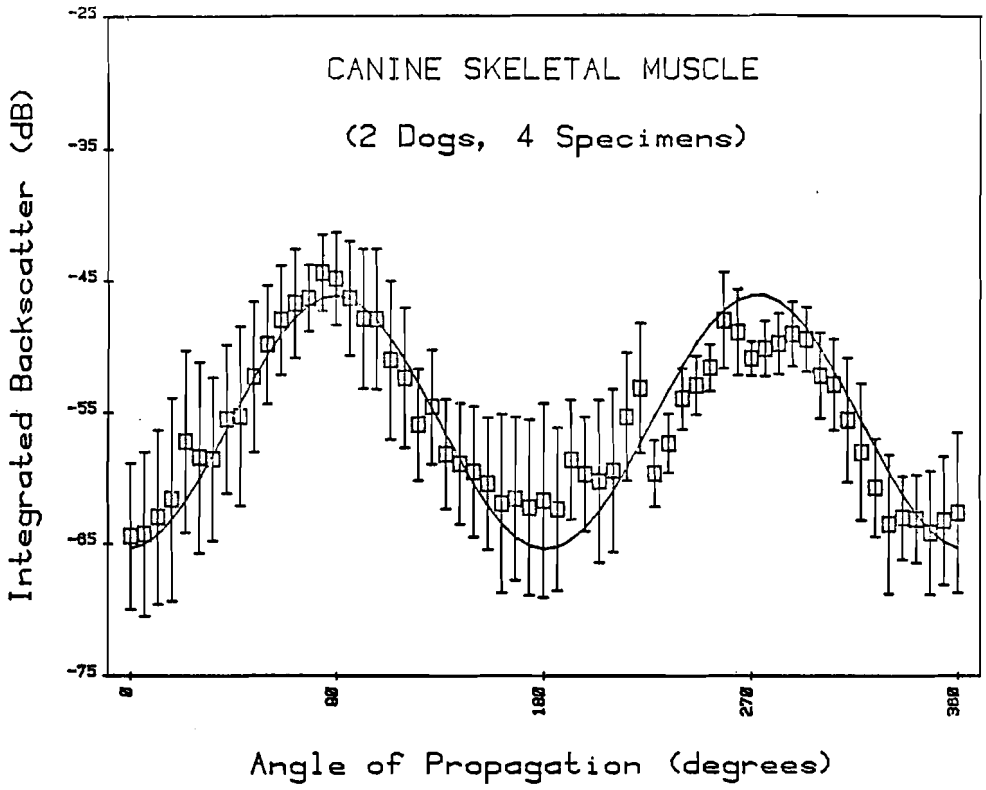

Figure 3. The integrated backscatter of canine skeletal muscle as a function of angle of propagation. The maximum to minimum difference is 22 dB.

B-6. Anisotropy of Ultrasonic Velocity in Soft Tissues

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A previous report from another laboratory[1] has demonstrated the existence of anisotropy in ultrasonic velocity, but the velocity has been reported in only two directions, parallel and perpendicular to the fibers of muscle. That report indicates that the magnitude of the anisotropy is on the order of 10 m/s in tissues having velocities of approximately 1550 m/s, with maximum velocity occurring along the fibers and minimum occurring parallel to the fibers. The objective of this project is to determine the magnitude and angular dependence, i.e., the degree of anisotropy, of the ultrasonic velocity in soft tissues.

To detail an anisotropy of 10 m/s in a 1 cm thick specimen demands measurements of time-of-flight differences on the order of ten ns. This resolution is beyond the capabilities of the current time-of-flight measurement system (PR 17, B-1; B-1), so we are investigating different technologies for submicrosecond interval measurement, such as phase-locked detection.

1. Chris R. Mol, "Ultrasound Velocity Tomography and Dynamic Cardiac Geometry," Ph.D., thesis, Interuniversity Institution of Cardiology, The Netherlands, 1981.

B-7. Adaptive Pulse-Echo Imaging for Ultrasonic Tissue Characterization

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Support: RR 00396

Conventional B-scan imaging systems focus signals received by phase-sensitive, linear arrays as if tissue were a homogeneous medium. Estimates of attenuation coefficient from such a beamformer are corrupted by the perturbation of wavefronts across the array caused by tissue inhomogeneities. Previously we described two equivalent causal models for representing dispersion and inhomogeneity in tissue. One, which is based on the Hilbert transform, assumes attenuation is a linear function of frequency (PR 16, B-5). The other, an all-pole model, can be synthesized from any experimental attenuation data (PR 17, B-4). Here we describe simulations which show that neglecting phase perturbations, which can occur in tissue, leads to substantial errors in measurements of attenuation with backscattered ultrasound.[1] The adaptive

beamforming techniques we developed for focusing when the medium is dispersive and inhomogeneous succeeded in correctly estimating attenuation (PR 16, B-5).

Previously we found the error of a homogeneous-medium beamformer in a simulation which included a single target in a 2-layer medium examined by a 3-element transducer. In the latest test we increased the number of elements in the transducer to 21 and reduced the spacing from 1 cm to 1 mm, which is representative of the arrays used in cardiac imaging. We also moved the target at constant radius along an arc from a position on axis to one 40 degrees off axis. The choice of a single target in the medium means that the only signals considered at the receiver were those which came from a single, small volume. In order to meet this condition we also examined adaptive focusing on transmission, as well as during reception.

For the test of beamforming on reception, the insonified volume was placed in the second layer of a 2-layer model. The layer nearest the transducer was 5 cm thick. Attenuation of the layers differed by a factor of 5; the index of refraction was 1.02. The signal emanating from the insonified volume was 3 cycles of a 6 MHz sine wave with a half-sine envelope. The distance to that volume was 11 cm. The error in the slope of attenuation versus frequency estimated from the output of the homogeneous-medium beamformer increased to nearly 80% as the insonified volume was moved off axis (Figure 1). The error of attenuation estimated using the output of our adaptive beamformers was less than 2%. Even greater differences were obtained with the tests of adaptive focus on transmission into a 3-layer model. We concluded that homogeneous-medium beamforming can introduce substantial and unacceptable errors into estimates of attenuation due to the perturbation of phase fronts across the transducer array.

The adaptive beamformers we used, provided relatively small but important corrections to the signal alignment of the homogeneous-medium beamformer. Successful adaptive beamformers were implemented in both the time and frequency domains. A matched filter was used in the time domain to estimate the actual delays from the scattering volume. The actual delays were then used to correct the homogeneous-medium delays. These corrections were less than 200 ns for the 2-layer model over the 40 degree viewing angle studied. The matched filter used to find the actual delays was applied only during an interval around the expected time of arrival of an echo from the insonified volume, as determined by the homogeneous-medium delays.

In the frequency domain the adaptive beamformer output was found by summing the magnitude of the frequency response of the signal from each array element, after aligning them with the delays expected in a homogeneous medium. Thus the transformation into the frequency domain was done before rather than after summation of element signals. The transform window must be long enough to contain the entire received signal. For the 2-layer model the window had to be 200 ns longer than the pulse duration to account for the misalignment of the homogeneous-medium beamformer outputs. Although this implementation is efficient and straightforward, it has the disadvantage that the actual delays are not available for adaptive focusing on transmission.

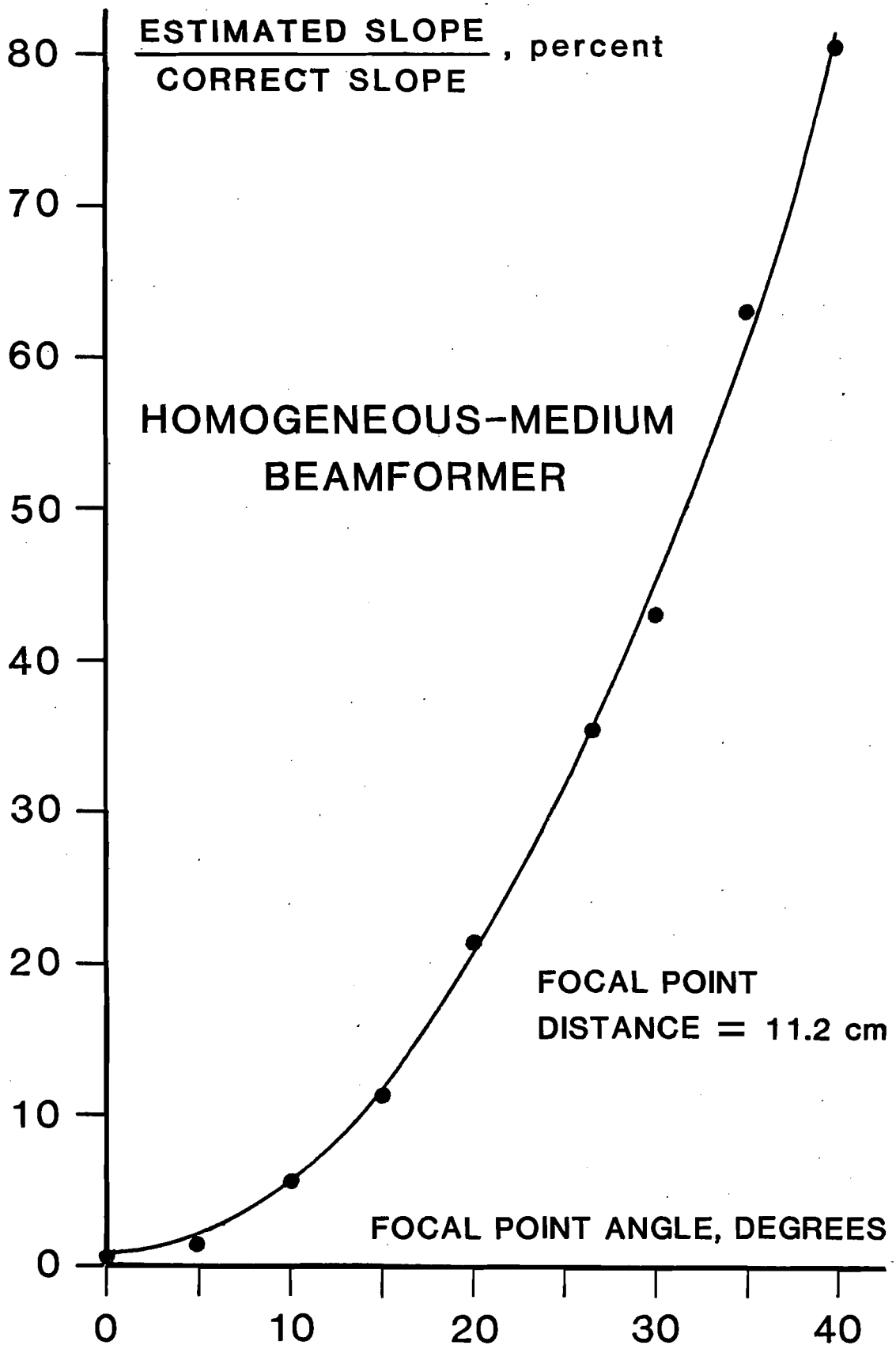

Figure 1. Error in estimating the slope of attenuation versus frequency of a 2-layer tissue model using the output of a homogeneous-medium beamformer.

In the next phase of this work we plan to test the adaptive beamforming schemes by measuring gelatin tissue mimicks, whose attenuation has been verified in transmission scanning (B-1). We will use a 15-channel latch-counter and driver circuit, which we designed and built to steer and focus the transmission into the gelatin (PR 17, B-5). Received signals from static targets will be acquired with a single-channel, dual-microprocessor echocardiograph which was also designed and built at the Biomedical Computer Laboratory (PR 15, A-17). Obviously, with a single-channel receiver beamforming must be done off line. Offline beamforming however, is not a drawback at this time because we must save the individual array-element signals in order to compare beamforming schemes.

1. K. V. Gurumurthy and R. M. Arthur, "An Adaptive Beamformer for Ultrasonic Tissue Characterization," Ultrasonic Imaging, vol. 4, pp. 184-185, 1982 (abstract).

B-8. Algorithm Development for Radiation-Treatment Planning

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Support: RR 00396
RR 01380
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We have continued our previously described (PR 17, B-6) software-development efforts for implementing the "delta-volume" method (PR 13, I-3; PR 14, G-6; PR 15, G-4; PR 16, B-14) of computing three-dimensional absorbed-dose distributions for radiation-treatment planning. To allow the published tissue-air-ratio data for water[1] to be used in our algorithms, we have transformed these data from the right circular-cylindrical coordinate system in which they are presented into the Cartesian system, and from the resulting values have computed a three-way table of differential scatter contributions to total dose. These tables were checked by comparing appropriate summations with the rectangular-field tissue-air-ratio values of Johns and Cunningham[1] obtained by them using the Clarkson sector method[2] to integrate their circular-field data.[1] The maximum relative deviation between values obtained by the two independent determinations was found to be 0.7 percent. We attribute this small difference, in part, to the approximate graphical-integration technique employed by the above-mentioned authors; our approach employed exclusively

analytical integrations. We expect that the newly computed water-data tables will lead to improved performance of our algorithms in future comparisons (B-9) of our computed distributions with phantom data.

An additional component of the algorithm that has been completed is the construction of a three-dimensional table representing the energy-average value of the linear-attenuation coefficient for cobalt-60 photons in water between any two 1-cm^3 voxels in a field measuring 16 x 16 x 16 cm^3. The Klein-Nishina electronic cross-section, computed as a function of the average primary-photon energy and of the appropriate scattering angle, was employed for these evaluations.

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

2. J. R. Clarkson, "A Note on Depth Doses in Fields of Irregular Shape," British Journal of Radiology, vol. 14, pp. 265-268, 1941.

B-9. Macromodule-System Implementation for Absorbed-Dose Calculations in Radiation-Treatment Planning

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Support: RR 00396
RR 01380
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The macromodule system previously described (PR 17, B-7) was used to calculate dose for the RANDO phantom with results that differed from measured data by about 2 percent for the central axis. Several potential sources of errors were identified, the main one arising from the approximations used in the conversion of the differential scatter-air ratio (SAR) data from the cylindrical to the rectangular system of coordinates employed in the algorithm. Before the dose could be recomputed with improved SAR tables, the macromodule hardware was severely damaged when the legs on the table supporting the hardware collapsed while the system was being moved. Cables, connectors, crates, and modules were all damaged. Rather than repair the modules and other equipment, and because the macromodule system had performed its primary task of demonstrating that the algorithm can be executed in a reasonable time on a relatively small system customized to the task, the functions of the macromodule hardware were programmed for a TI-980 computer and a two-computer system

was assembled to perform the dose calculations. Although this system requires about 4 hr instead of the 8 min for the system containing the macromodules, it will be useful for future algorithm evaluations.

B-10. Three-Dimensional Display of Absorbed-Dose Computation for Radiation-Treatment Planning

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Support: RR 00396
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A small program was written to convert the calculated dose from the format previously developed (PR 13, I-3; PR 14, G-6; PR 15, G-4; PR 16, B-14; PR 17, B-6) to the format required by the COMPOSE[1] program used for manipulation and display on MMS-X[2] systems, thus making available all of the capabilities of the COMPOSE program such as interactive image editing and plotter output. Plans for the next year include comparing displays of calculated dose data using three-dimensional contours of constant intensity and serial sections with the dose as the third coordinate.

1. J. P. McAlister, "Program COMPOSE," Technical Memorandum 292, Computer Systems Laboratory, Washington University, St. Louis, Missouri, December 1981.

2. C. E. Molnar, F. U. Rosenberger, and R. J. 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-11. Integrated-Circuit Implementations for Absorbed-Dose Calculations in Radiation-Treatment Planning

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Support: RR 00396
RR 01380
Washington University

The design of a custom integrated circuit to facilitate dose calculations for radiation-treatment planning has been started as a test vehicle for the CSL IC design facility and to provide a system for extensive evaluation of the "delta-volume" method for dose calculation (B-8; PR 13, I-3; PR 14, G-6; PR 15, G-4; PR 16, B-14; PR 17, B-6). The chip is being designed to perform the computation-intensive part of the dose calculation and will require an environment including a moderate-size memory and a general-purpose computer to supply inputs to the chip, harvest the results, and perform some of the less frequent but more complex computations.

An internal bus structure, a floor plan, and an instruction set for the custom chip have been developed; these have allowed estimates of the size and performance of the chip to be made. The chip size will be about 4.6 mm by 2.6 mm and will have a cycle time of about 400 ns. The estimated computation times for several treatment volumes are listed below:

Size, cm^3	Time, sec
8 x 8 x 16	3.3
16 x 16 x 16	52
16 x 16 x 32	410
32 x 32 x 32	6500

As can be seen from the table, clinically useful computation times can be achieved for volumes up to about 16 x 16 x 32 cm^3. Times for larger volumes are long enough to restrict their use to research or to occasional applications. Plans for the coming year include completion of the detailed design of the chip and its fabrication.

B-12. PETT Experimental Studies

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J. Markham, BCL
A. L. Rand, B.S., Medicine
B. E. Sobel, M.D., Medicine
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Support: RR 00396
RR 01380
HL 13851
HL 17646

The overall goal of this project is to implement and evaluate procedures required to translate to intact animals the results obtained with selected positron-emitting tracers used to characterize myocardial metabolism and perfusion in isolated hearts and anesthetized, open-chest dog studies. Utilizing positron-emission tomography, distribution of tracer and the time course of its uptake and clearance from the myocardium can be quantified. Such studies are intimately related to the clinical activities being undertaken with PETT IV and SUPER PETT I.

A recently completed study demonstrated that viable, but ischemic tissue could be detected and localized in vivo by sequential detection of the washout of ^{11}C-palmitate. In the absence of coronary stenosis, clearance of tracer was homogeneous throughout the heart. With critical stenosis sufficient to induce ischemia without infarction, however, regional ^{11}C-clearance became heterogeneous under control conditions and was more strikingly so with induced tachycardia. Thus, sequential positron-emission tomography after injection of ^{11}C-palmitate may be useful clinically in delineating zones of viable but ischemic myocardium.

In the past year, the use of thrombolytic therapy to non-surgically revascularize myocardium after acute myocardial infarction has become clinically feasible. To determine whether such an intervention results in actual salvage of myocardial metabolism,[2] anesthetized, intact dogs were studied in which coronary thrombosis was induced by placement of a copper coil in the left anterior coronary artery. Thrombolysis was induced by the administration of intracoronary streptokinase (4000 U./min) 1-14 hrs after occlusion. Positron tomography after the administration of ^{11}C-palmitate was performed prior to and 90 minutes after thrombolysis. The results of these studies demonstrated that although angiographically demonstrable coronary revascularization is possible and flow (measured with microspheres) returns to greater than 60% of normal up to 14 hours after coronary occlusion, salvage of myocardial metabolism in the area at risk occurs only when revascularization occurs within the first six hours of the thrombotic episode. Furthermore, quantitative evaluation of cardiac tomograms demonstrated that maximum salvage occurs, as would be expected, when the ischemic time is short. The results of this study demonstrate that to be effective, coronary thrombolysis must be instituted

early after the occlusive event. In addition, this study demonstrates the usefulness of sequential positron tomography in assessing the efficacy of therapeutic interventions. The protocol developed for this experimental study has been utilized subsequently in the evaluation of patients with acute myocardial infarction who are candidates for coronary-thrombolysis.[2-4]

In addition to our studies with ^{11}C-palmitate, a project completed in the past year evaluated the usefulness of using $H_2{}^{15}O$ as a perfusion indicator. In these studies, 5 anesthetized dogs were subjected to coronary occlusion by placement of a copper coil in the left anterior descending coronary artery. $H_2{}^{15}O$ was given intravenously, and after a 20 second delay, cardiac positron-emission tomographic data was acquired for 40 seconds. Since water circulates in the vascular space, in order to define myocardial radioactivity, we used a $C^{15}O$ to define the vascular space. Tomograms obtained after $H_2{}^{15}O$ administration were corrected for radioactivity in the vascular space. To determine whether the regional myocardial distribution of $H_2{}^{15}O$ is an estimate of flow, dogs were then given a bolus, via the left ventricle, of aggregated albumin microspheres labeled with the positron-emitting tracer ^{68}Ga. Subsequent tomographic data were collected, and regional water distribution was compared to regional microsphere distribution. The results indicate a good correlation ($r = .92$) over the range of flows studied and indicate that regional tissue water can be used to estimate myocardial perfusion.[5] Experiments in the coming year will define more precisely the effects that vascular pool activity as well as movement and partial volume effects play in the definition of regional $H_2{}^{15}O$ distribution detected non-invasively. In addition, experiments must be performed to define whether tissue:blood coefficients change in regions of myocardium that are subjected to ischemia or other forms of cardiac disease.

In addition to the studies involving measurement of regional myocardial metabolism and perfusion, studies have been completed in the past year to define further the sources of error in tomographic measurements. In particular we are concerned with the effects of cardiac motion induced by both intrinsic systolic/diastolic movement as well as movement in the Y and Z axes induced by nonsynchronous, respiratory motion. In humans, this motion is in the order of 1.5 cm. Therefore, myocardium can move through 1 tomographic plane and thus, markedly influence apparent radioactivity and morphology. To evaluate the influence of both cardiac and respiratory motion, 5 dogs were studied after an administration of ^{11}C-palmitate. Tomographic data were acquired during normal cardiac motion and respiration, after cardiac arrest induced by potassium chloride but with maintained respiratory motion (by ventilating the animal under positive pressure), and after the respirator was stopped. The results of these studies indicate that significant image degradation occurs due to both intrinsic cardiac as well as respiratory motion. Thus, quantitative tomography must gate for both of these intrinsic motions of the heart, as well as correct for partial volume effects.[6,7]

During the coming year, we plan to define the usefulness of sequential cardiac PET further in order to demonstrate the restoration of myocardial metabolism after thrombolytic therapy using dynamic acquisition (in SUPER PETT-I). We further plan to define the usefulness of cardiac and respiratory gating in obtaining quantitative tracer information. Finally, we hope to refine the

use of $H_2{}^{15}O$ in the measurement of myocardial perfusion so that not only can regional measurements of myocardial perfusion be defined, but also absolute quantitation of flow can be made.

1. R. A. Lerch, H. D. Ambos, S. R. Bergmann, M. J. Welch, M. M. Ter-Pogossian, and B. E. Sobel, "Localization of Viable but Ischemic Myocardium by Positron Emission Tomography (PET) with ^{11}C-palmitate," Circulation, vol, 64, pp. 689-699, 1981.

2. S. R. Bergmann, R. A. Lerch, K. A. A. Fox, P. A. Ludbrook, M. J. Welch, M. M. Ter-Pogossian, and B. E. Sobel, "The Temporal Dependence of Efficacy of Intracoronary Thrombolysis Assessed by Positron Tomography," American Journal of Medicine, in press.

3. B. E. Sobel and S. R. Bergmann, "Coronary Thrombolysis: Some Unresolved Issues" (Editorial), American Journal of Medicine, vol. 72, pp. 1-4, 1982.

4. B. E. Sobel, E. M. Geltman, and S. R. Bergmann, "Quantitative Assessment of Infarct Size and its Influence by Thrombolysis," Proceedings of the IX World Congress of Cardiology, in press.

5. S. R. Bergmann, K. A. A. Fox, A. L. Rand, K. D. McElvany, M. M. Ter-Pogossian, and B. E. Sobel, "Non-invasive Measurement of Regional Myocardial Perfusion by Positron Tomography," Circulation, submitted (abstract).

6. M. M. Ter-Pogossian, S. R. Bergmann and B. E. Sobel, "Influence of Cardiac and Respiratory Motion on Tomographic Reconstructions of the Heart: Implications for Quantitative Nuclear Cardiology," Journal of Computer Assisted Tomography, in press.

7. B. E. Sobel and S. R. Bergmann, "Cardiac Positron Emission Tomography," International Journal of Cardiology, in press.

B-13. PETT IV Cardiac Studies

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E. M. Geltman, M.D., Medicine
J. Markham, BCL
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M. J. Welch, Ph.D., Radiology

Support: RR 00396
RR 01380
HL 13851
HL 17646

This project was designed to determine whether positron-emission tomography (PET) permits quantification of regional myocardial metabolism in vivo in normal subjects, patients with ischemic heart disease, and patients with cardiomyopathy. Previously, we have demonstrated that ^{11}C-palmitate accumulates homogeneously in the myocardium of normal subjects, accumulates poorly in regions of infarcted myocardium, and accumulates in a subjectively heterogeneous manner in patients with congestive cardiomyopathy. We have also demonstrated both in experimental animals and in patients that the extent of the region of depressed accumulation of palmitate in myocardium observed after myocardial infarction is quantifiable by PET, and that estimates of infarct size determined by PET correlate closely with enzymatic and morphometric estimates of infarction at necropsy in experimental animals and with enzymatic estimates of infarction in patients. Furthermore, previous studies in patients have shown a close concordance between the electrocardiographic locus of infarction and the locus of infarction detected by PET. The extent of regional metabolic derangement determined by PET also correlated closely with the extent of depression of left ventricular function detected by radionuclide ventriculography in patients with both anterior and inferior myocardial infarction.

During the past twelve months research activities have focused on several problems: (1) quantification of the extent and nature of regional myocardial metabolic abnormalities in patients with congestive cardiomyopathy; (2) determination of the natural history of the extent and distribution of myocardial injury during the first fourteen days after myocardial infarction; (3) assessment of the efficacy of orally administered nifedipine, a calcium antagonist, and intracoronary streptokinase 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); and (4) determination of the physiologic basis for reciprocal electrocardiographic ST-segment depression observed early after myocardial infarction.

A total of seventeen patients with congestive cardiomyopathy, thirteen normal subjects, and six patients who had survived an initial transmural myocardial infarction were studied with positron emission tomography after the intravenous administration of 12 to 20 mCi of ^{11}C-palmitate. Regional

depression of the accumulation of ^{11}C-palmitate was assessed, characterized and quantified in seven parallel transverse reconstructions in each patient. Algorithms were developed, validated and implemented to assess-quantitatively the spatial heterogeneity previously described only in a subjective manner. Normal subjects exhibited homogeneous accumulation of ^{11}C-palmitate within the left ventricular myocardium with smooth transitions in regional content of radioactivity. Patients with cardiomyopathy exhibited marked spatial heterogeneity of the accumulation of palmitate throughout the myocardium, easily distinguishable from normal subjects and a pattern distinct from that observed in patients with transmural infarction in whom discrete regions of depressed accumulation of palmitate were observed with residual viable myocardium accumulating palmitate homogeneously (Figure 1). Patients with cardiomyopathy exhibited a larger number of discrete non-contiguous regions of accumulation of palmitate within myocardium than did control subjects or patients with transmural infarction [17.4 $\pm$ 0.6(SEM) vs 11.8 $\pm$ 0.7 vs 10.3 $\pm$ 0.6, $p < 0.005$]. Similarly, regions of accumulation of palmitate were irregularly shaped in patients with cardiomyopathy, with longer normalized perimeters than either control subjects or patients with transmural infarction (2.0 $\pm$ 0.05 vs 1.8 $\pm$ 0.06 vs 1.9 $\pm$ 0.09, $p < 0.05$). Similarly, the skewness of the frequency of distribution was significantly different between normal subjects and patients with cardiomyopathy. These differences in the accumulation of ^{11}C-palmitate could not be explained by regional differences in left ventricular wall motion or myocardial perfusion. Studies are currently underway to evaluate the rates of extraction and disappearance of ^{11}C-palmitate from myocardium of normal subjects, patients with infarction, and patients with cardiomyopathy employing SUPER PETT I which will permit the high time resolution studies which are necessary for accurate assessment of the dynamics of myocardial metabolism.

In order to determine the interval after the apparent onset of myocardial infarction during which the evolution continues and salvage remains possible, PET was performed after the intravenous injection of ^{11}C-palmitate in 26 patients at selected intervals early after onset and later after completion of infarction. In 9 patients initially studied 7 to 18 hours after the onset of pain, infarct size averaged 60 $\pm$ 11 PET-gram-equivalents-and did not change over the ensuing 2 weeks (57 $\pm$ 12). In 7 patients studied 24 to 72 hours after symptom onset (mean = 45.1 hours), infarct size averaged 31 $\pm$ 7, again remaining unchanged later (29 $\pm$ 10). In 10 patients initially studied 3 to 40 days after the onset (mean = 13.4 days) infarct size estimated by PET initially and subsequently remained constant (56 $\pm$ 10 and 55 $\pm$ 12), with values from the 2 studies correlating closely ($r = .93$).

PET estimates of infarct size are being employed as the primary endpoint of studies designed to assess the efficacy of orally-administered nifedipine and intracoronary streptokinase infusions for the salvage of ischemic myocardium when administered within the early hours after myocardial infarction. The results of studies with streptokinase are discussed in project A-8. All patients had tomographic procedures performed immediately after randomization prior to the initiation of drug therapy, with repeat imaging 7 to 12 days later. The response of patients randomized to placebo was comparable to that described above with essentially no change in the size of the tomographic defects detected during the first 14 days after infarction. Of the 7 patients randomized

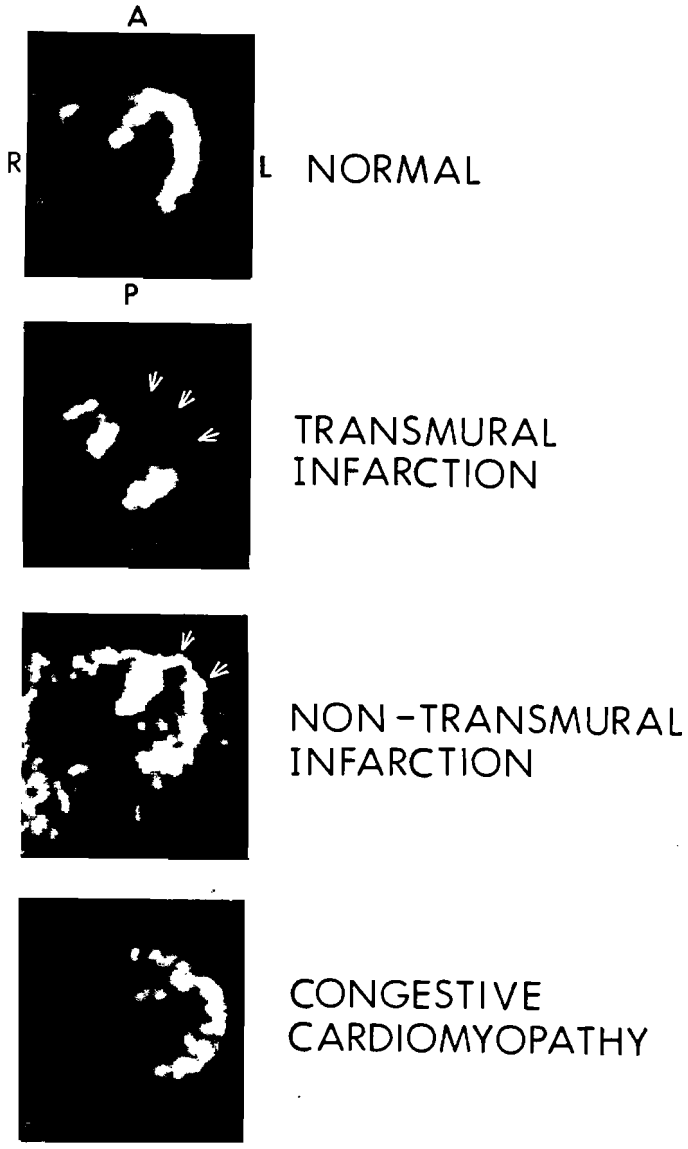

Figure 1. Shown here are representative mid-ventricular reconstructions obtained with PETT IV after the i.v. injection of ^{11}C-palmitate from a normal subject, patients with transmural and nontransmural infarction and congestive cardiomyopathy. The region of accumulation of ^{11}C-palmitate is homogeneous in the normal subject, demonstrates a region of intense homogeneous depression of the accumulation of ^{11}C-palmitate after transmural infarction, and less intense, less homogeneous depression after nontransmural infarction. The patient with congestive cardiomyopathy demonstrates marked spatial heterogeneity of the distribution of ^{11}C-palmitate within myocardium.

to nifedipine therapy, 2 demonstrated a marked diminution in the size of the region of depressed accumulation of palmitate (50 and 25% reductions). In 4 patients the size of the defect was comparable (change $\leq$ 10%) in the early and late tomographic studies. In one subject the apparent region of metabolic abnormality increased by 20%. Overall, PET infarct size was 83.6 $\pm$ 16 at the time of the initial study and 78.2 $\pm$ 17.6 in the repeat tomographic study. The study is ongoing with a planned recruitment of 25 patients in treatment and control groups.

Reciprocal ST-segment depressions are commonly observed during acute myocardial infarction. However, their physiologic cause remains in dispute. To determine whether reciprocal ST depression is caused by ischemia distant from the primary locus of infarction or simply to an electrical phenomenon, 15 patients with initial infarction (5 anterior and 10 inferior as localized by electrocardiographic criteria) were evaluated by positron emission tomography with ^{11}C-palmitate within 27 hours [9.5 $\pm$ 7.1(SE)] of the onset of pain and again 11.5 $\pm$ 2.2 days later. Coronary angiography was performed in 12 patients within 6 months of infarction. Significant reciprocal ST-segment depression in initial electrocardiograms was defined as $\geq$ 1 mm ST depression in $\geq$ 2 leads. Eight patients exhibited such depression. Only 2 exhibited decreased accumulation of palmitate in a zone other than the primary zone of infarction. In both, the remote zone of decreased uptake was distal to significant coronary narrowing. Late resolution of the tomographic abnormality occurred in one of these 2 patients. Only 1 of the 7 patients without reciprocal ST depression had decreased accumulation of palmitate in a region distant from the infarct. Thus, reciprocal ST depression early after the course of acute myocardial infarction does not usually reflect ischemia and its metabolic sequelea in a region distant from the primary site of infarction.

B-14. Processing of PETT IV Images

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Support: RR 00396
RR 01380
HL 17646

Previous studies in man have demonstrated a close correlation between enzymatic estimates of infarct size and PETT IV tomographic estimates of infarct size obtained following intravenous injection of ^{11}C-palmitate in patients with anterior transmural and inferior infarction (PR 17, B-10). Delineation of the regions of diminished ^{11}C-palmitate uptake, required for the tomographic estimation of infarct size, is frequently hampered by the poor quality of the PETT IV images. Edge detection is a common problem in nuclear medicine, and the various image processing techniques which are used there may be applicable to the PETT IV images.

Our attempts to improve the detectability of infarcted regions focused first on the effects of the attenuation correction. Since the attenuation correction factors are calculated as the ratio of the projection data obtained from two transmission scans, this correction introduces substantial noise in the reconstructed images. Alternative algorithms for computing attenuation, such as utilizing a few selected regions of uniform attenuation, significantly increase the execution time required by the reconstruction process. We decided to smooth the attenuation data rather than use another algorithm because smoothing can be performed rapidly. Although previous algorithms used here have smoothed the attenuation factors, we found that the best results were obtained by smoothing the projection data for the two transmission scans before computing the ratio (attenuation factors). However, we found that the projection data could not be smoothed by using data from different projection angles as this resulted in swirling patterns in the reconstructed transmission and emission images. A simple 1-2-1 algorithm applied along the projection data did not significantly reduce resolution since the projection samples are 0.5 cm apart, and the reconstructed resolution is about 1.5 cm. After implementation of the attenuation smoothing, it was decided that further investigation of image processing techniques should be delayed until SUPER PETT I is available.

B-15. Interactive Studies of Regions of Interest in PETT IV Images

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HL 17646

The original system designed to allow users to study arbitrarily shaped regions of interest in PETT IV images (PR 17, B-9) has been implemented successfully along with the enhancements alluded to in (PR 17, B-9). The current system allows a user to construct and display up to five arbitrary regions. These regions are then encoded and stored on disc so that they are available for subsequent processing on various images.

A post-processing system for these specific regions also was implemented to aid in mathematical analysis. For each region, the post-processing software calculates:

1) total number of pixels within the region;
2) total activity within the region;
3) average activity per pixel;
4) variance of the activity;
5) standard deviation of the activity;
6) volume enclosed by the region;
7) maximum of the region;
8) skewness of the region;

9) kurtosis of the region;
10) total coastline;
11) normalized coastline.

The post-processing software also allows a user to specify a percentage interval to be displayed within the specified region. When this percentage interval is displayed, it is possible to determine the number of non-contiguous regions formed by a particular iso-count threshold. Analysis of many iso-count thresholds and the coastline parameter allows a crude but effective measure of the relative homogeneity of a particular region within the image.

This technique was applied to a group of patients with congestive cardiomyopathy along with a group of normal subjects. Results of this study currently are in press.[1]

Currently, work is underway to move this software system to a Perkin Elmer 3200 series machine which will replace the Interdata 7/16 in the near future.

1. E. M. Geltman, J. L. Smith, D. E. Beecher, M. M. Ter-Pogossian, and B. E. Sobel, "Altered Regional Myocardial Metabolism in Congestive Cardiomyopathy Detected by Positron Tomography," American Journal of Medicine, in press.

B-16. In-Vivo Measurements of Regional Blood Flow and Metabolism in Brain

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We have continued our previously reported (PR 17, B-11) 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; PR 17, 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.

We have adapted the autoradiographic method of Kety et al.[1] for measurement of regional cerebral blood flow for use with positron-emission tomography (PET). To investigate the validity of this model, we employed computer simulations to study its behavior in relation to tissue inhomogeneity, input-function shape, effects of local pathology, and errors in data acquisition. Our simulations show that inaccuracies in timing the arterial input function can cause large errors in the estimated flow but variations of the remaining factors introduce only small errors in the estimates of flow. Experimental procedures have been implemented to ensure accurate timing of the input function.

Estimates of flow computed on the basis of the Kety model from PET scans obtained within 40 sec after the start of the input injection correlate with estimates of flow obtained from other methods. However, scans performed after the initial 40-sec period following injection lead to significantly lower estimates of flow, a discrepancy that has been noted by other investigators. This discrepancy is probably due to the inadequacy of the Kety model which assumes that the vascular space and tissue can be viewed as a single entity. We are investigating the use of more complex models which will allow longer PET scans without loss of accuracy in the estimated flow.

An important index of central nervous-system function is oxygen-utilization rate. Our intent is to use $^{15}O_2$ as a tracer for regional measurements, capitalizing on the success in this endeavor that has already been achieved[2] using collimated external-detection systems having relatively high temporal resolution (~ 0.1 sec). With the positron-emission tomographic systems we plan to employ in these studies, however, achievable temporal resolutions are more modest (~ 40 sec). This limitation places restrictions on the number of parameters that can be estimated from the data, and hence, in the level of detail in the models used to interpret the results. As a basis for simulations serving to evaluate the performance of the simple compartmental models that in practice must be employed, we are developing a detailed distributed model of oxygen transport and utilization at the capillary level. Our model is a generalization of Krogh's analysis,[3] and extends his steady-state description of the radial distribution of oxygen in a single cross-sectional plane of a tissue cylinder surrounding a capillary to include axial and temporal dependencies. Our model takes into account the effect of axial variation in hemoglobin saturation as a result of progressive depletion of oxygen in blood flowing along the capillary from the arterial end. We have obtained the steady-state solutions of our equations applicable to the description of systemic-oxygen distributions; efforts to find time-dependent solutions for $^{15}O_2$ are in progress.

1. S. S. Kety, "Measurement of Local Blood Flow by the Exchange of an Inert, Diffusible Substance," in Methods in Medical Research, vol. 8, H. D. Brunner, ed., Chicago, Year Book Publishers, 1960.

2. M. M. Ter-Pogossian, J. O. Eichling, D. O. Davis, and M. J. Welch, "The Measure In Vivo of Regional Cerebral Oxygen Utilization by Means of Oxyhemoglobin Labeled with Radioactive Oxygen-15," Journal of Clinical Investigation, vol. 49, pp. 381-391, 1970.

3. A. Krogh, "The Number and Distribution of Capillaries in Muscles with Calculations of the Oxygen Pressure Head Necessary for Supplying the Tissue," Journal of Physiology (London), vol. 52, pp. 409-415, 1919.

B-17. PETT Time-of-Flight Data Acquisition System Development

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HL 25944

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 I, utilizing scintillators of cesium flouride (CsF) and a high-speed acquisition and pre-processing system, employs information about the differential time-of-flight (TOF) of annihilation photons to achieve a significant sensitivity improvement over conventional PETT systems such as PETT IV and PETT VI.[1] A number of data collection and processing strategies are summarized in (PR 17, B-14) and in reference 2.

As annihilation events are detected and encoded, one of two collection modes is implemented. In the "pre-processing" mode, pre-images[2] are built in real-time as data are being collected. This process includes both TOF correction and sensitivity normalization for detector variations, attenuation correction, cell-position calculation and incrementing of cell values. Seven slice processors operating in parallel perform this function by processing events on a per-viewing slice basis. The primary advantage of this mode is a very significant reduction in processing time. In the "list mode," raw event data are channeled unaltered via the list queue to the host computer

where they are saved in mass storage. The advantage of this mode is extreme flexibility in selection of processing and reconstruction modalities. For example, clinical studies can benefit from the ability to perform retrospective temporal gating of data. Engineering studies benefit from the ability to implement virtually any conceivable reconstruction algorithm.

Electronics for the list mode have been developed and have been operational since May 1982. A prototype slice processor has been built and is presently being debugged. It is designed to operate on conventional projection and most-likely-position pre-image[2] and to do a high-speed final image reconstruction following data collection. An architectural design has been completed for an enhancement to the slice processor which would operate on confidence-weighted pre-images.[2] This design was motivated by theoretical predictions[3] of resulting superior image quality.

1. M. Yamamoto, G. R. Hoffman, D. C. Ficke, and M. M. Ter-Pogossian, "Imaging Algorithms and Image Quality in Time-of-Flight Assisted Positron Computed Tomography: SUPER PETT I," The IEEE Proceedings of the International Workshop on Time-of-Flight Emission Tomography, Washington University, St. Louis, Missouri, May 17-19, 1982, in press.

2. G. J. Blaine, D. C. Ficke, R. E. Hitchens, and T. J. Holmes, "Data Acquisition Aspects of SUPER-PETT," IEEE Transactions on Nuclear Science, vol. NS-29, no. 3, June 1981.

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, June 1981.

B-18. Software Support for SUPER PETT I

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Support: RR 00396
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HL 13851
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SUPER PETT I, one of the first time-of-flight assisted positron cameras developed, was successfully interfaced to a Perkin Elmer computer system and is currently being tested. This is the first time a scanner of this complexity has been interfaced at this institution, and that complexity lead to some special problems concerning initial software support and development. The three areas of support this report addresses are: Initial Communication, Collection Programs, and Verification of Data Received.

Initial Communication

At the time of this development, the SUPER PETT I camera, with its associated hardware, had been assembled and debugged as much as possible without actually installing the hardware interface on the host. The next step in development was installing the interface into the host computer and attempting to verify the operations of the scanner.

At this level of debugging, a desirable piece of software should serve as a low-level communication medium between the hardware specialist and the PETT interface, providing direct operator initiation of interface commands. That is, this software should serve as a convenient means by which one can converse with the PETT interface (and ultimately the camera), in a very low-level manner and "say" only what one wants to say, nothing more and nothing less.

With those requirements in mind, a software tool has been developed to allow this mode of communication. The options this software allows are necessarily designed around the basic, privileged Input/Output instructions of the digital computer used to support SUPER PETT I. (In this case the machine was a Perkin Elmer 7/32 and later the Perkin Elmer 3242.) Since the device interface is half-word oriented, all commands deal exclusively with a half-word "packet" of information. The basic operations to the user include: Status Request, Read Data, Write Data, and Write Command. Not surprisingly, all of the above options map directly into the Input/Output instructions of the aforementioned host computer.

The main use of this software is diagnosing problems with the PETT device at a very low level. If data packets received from the device are hard to understand and data-packet construction is cumbersome, this tool would be a failure. Careful attention was therefore paid to the human interface aspects of this software tool.

Communication to any device consists of regularly constructed bit and byte patterns which must be easily understood and constructed by the user who is doing the diagnosing. For this reason the communication is centered around a full screen display (Figure 1), which allows the formation of arbitrary half-words on a bit-by-bit basis. It also displays the data received from the device in a similar manner. This technique has proven to be optimal given the particular environment in which we are working.

Collection Programs

At the time of this development, the scanner and associated interface had been debugged down to the transfer level. The next logical step was that of retrieving list-mode data from the device and storing that data on a host computer disc pack. The overwhelming concern is speed. The PETT system is capable of generating large amounts of list-mode data in a very small time. Our major constraint is that of the prolonged transfer rate to a single disc, which is currently on the order of 833 Kbytes/second. This figure is based on benchmark tests which were run on our system configuration.

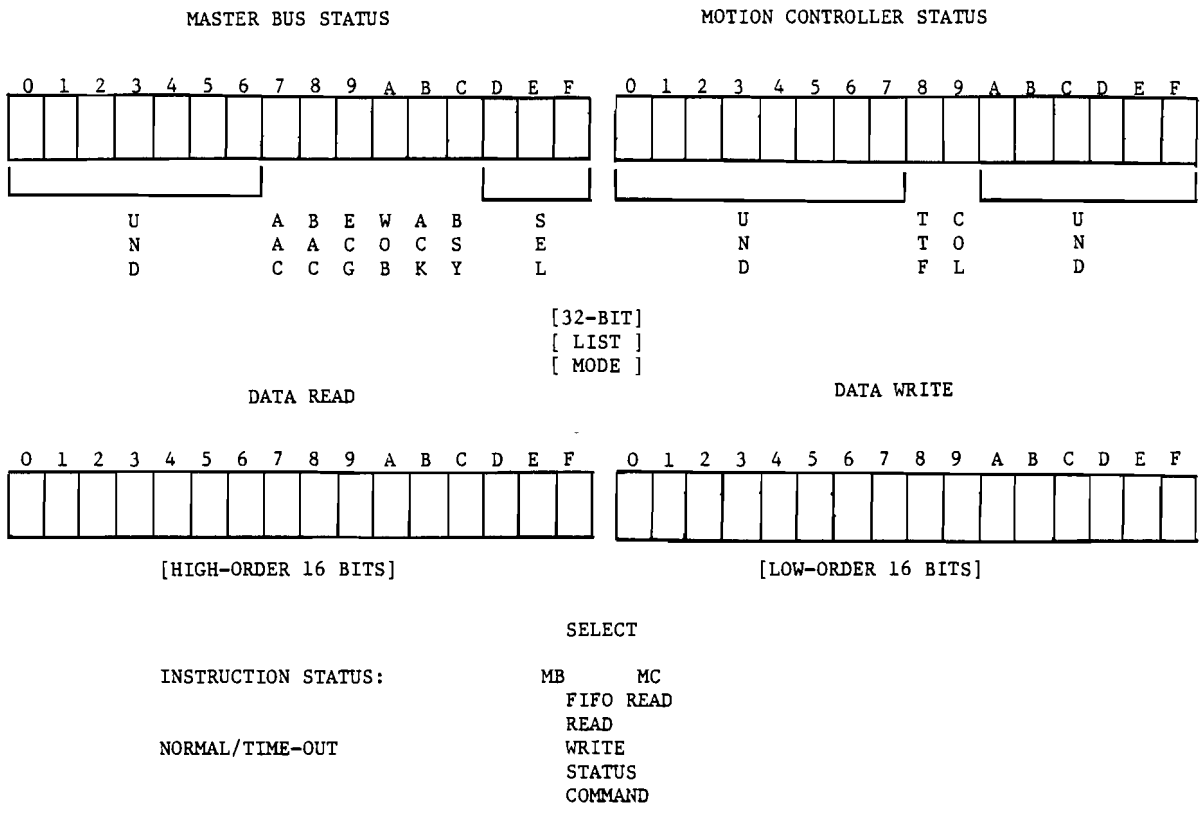

Figure 1. Full Screen Display. SUPER PETT I: Interface Debugging Software.

Initial connection programs were written using a programmed I/O approach. Each 16-bit half-word transfer required processor interaction. This approach was useful for initial data verification, but much too slow to be considered for the transfer of large amounts of list-mode data (the amount of list-mode data contained in a single scan typically exceeds 200 Mbytes). The next approach we considered was direct-memory-access (DMA) transfer. With this approach we can realize transfer rates which approach that of the maximum prolonged-transfer rate of the disc drive (~ 833 Kbytes/second).

Another problem encountered was that of sustaining a near continuous data transfer from the PETT device. It would be very undesirable to cease all data transfer from the device while we wait for a disc write to finish. This would lead to a very uneven sampling of the list/mode events. This problem was overcome by using a ring buffer and disc writes with the proceed option (this simply starts the write and immediately returns). This approach ensures a near continuous data transfer from the device with very little dead time between buffer switches. A basic flowchart of the final collection is shown in Figure 2. The dead time (the time we are not collecting real-time events) would consist of the time "wasted" between the flowchart symbols labeled A and B in Figure 2. This is just the time it takes to start a disc write and the time it takes to see if the next buffer has been transferred. If we assume that each buffer will have been transferred completely to the disc by the time we are ready to fill it again, then this check occurs only once. The actual time required for the Input/Output request and the buffer check is ~10.5 μsec, which is very small indeed.

The scheme outlined above delivers transfer rates of just under 800 Kbytes/second from SUPER PETT I, very close to the maximum prolonged rate to a single disc drive. The current bottleneck in the transfer rate stems from the physical link between the PETT device and the host computer. However, a small hardware change to the interface to utilize the high-speed protocol mode would allow transfer rates that would easily saturate the disc. Given current disc technology, there is not much to be gained from such a change now.

Verification of Data Received

After reasonable amounts of data could be collected in relatively short periods of time, it was important to have some method of looking at the individual event words from the PETT device. A single event word contains eight fields which completely describe a coincidence event in the system with time-of-flight information. If we had some way of collectively looking at these events, we could verify the information contained therein. The intent of this software is to provide a first level of event verification. For a given block of list-mode data, this software allows the user to interactively fix certain fields within the event word with minimum and maximum values. The entire block of list-mode data is then scanned, and a report is generated about the data that fell within the constraints. The report takes the form of a histogram of the arbitrary but user selected field. This software was mainly used for plotting time-of-flight information from single detector pairs.

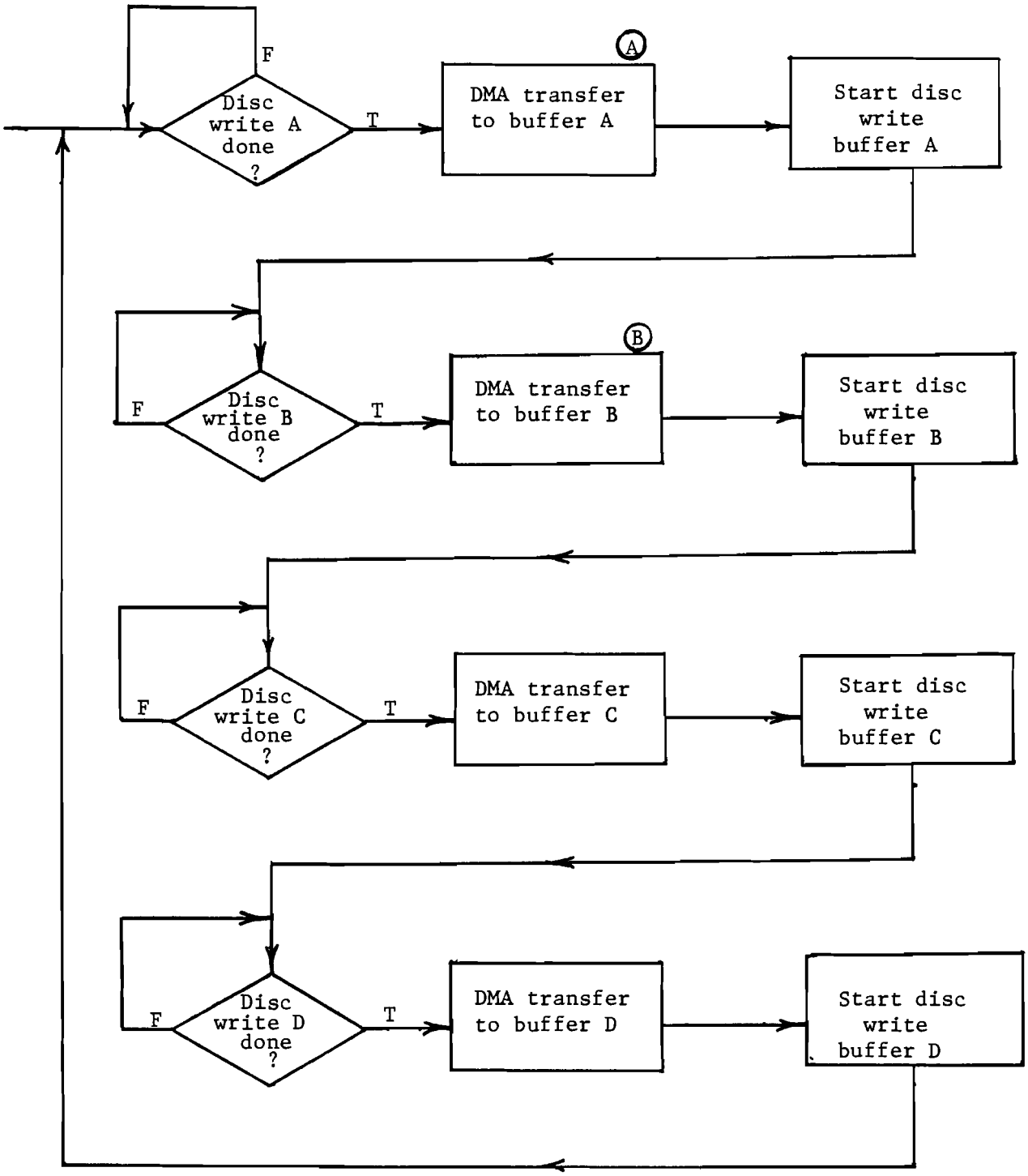

Figure 2. SUPER PETT I. Direct-Memory-Access Transfer Scheme.

B-19. Image Reconstruction Algorithm Using List Mode Data of SUPER PETT I

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Support: RR 00396
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HL 13851
HL 25944

We succeeded in getting the first cross-section images of the distribution of a positron-emitter in a human body using time-of-flight information, which was taken by SUPER PETT I,[1-3] employing the following algorithm.[2] This algorithm is used for patient scans.

Currently, data are collected in a list-mode format, as is shown in Figure 1. Information in each event word is converted (binned) to a 3-dimensional (3D) sinogram address $s(t,d,\theta)$. The data at that address are then incremented by one, making a 3-D histogram $s(t,d,\theta)$, where t is the TOF-information, d is the distance between the coincidence line and the system center, and θ is the angle of the coincidence line. The scales are 12 mm, 3.5 mm, and 1.875 degrees per bin, respectively, for t,d, and θ in the low resolution mode.

In the binning process, shown in Figure 2, at least two additional processes related to the TOF information are needed for the TOF image reconstruction: 1) In each detector pair, the TOF information is offset to some degree. This offset must be detected and corrected.[3-4] 2) The direction of the TOF-axis output by hardware does not fit with the direction expected by the reconstruction program. The direction of the output data must be inverted for some detector pairs.

We use two lookup tables to speed up the binning process: 1) The lookup-table address is in bits 13 to 31 of the event word in Figure 1. The data in the table give θ and d, and the highest bit is a mark for the TOF direction inversion. 2) The second lookup-table address is found in bits 9 to 24 of the event word. The data in the table give the TOF-offset values. The maximum speed of the binning process in the host computer is about 20 μsec/count for the TOF reconstruction and 10 μsec/count for conventional (non-TOF) reconstruction. Once the 3-D sinogram is obtained, corrections for sampling density, random coincidence subtraction, detector pair sensitivity, attenuation, etc. are applied.

A 1-D Gaussian filter, $G_1(T)$, along the TOF-axis is applied to the corrected 3-D sinogram to optimize the signal-to-noise ratio in the final image. It has been shown that 1-D Gaussian filtering is sufficient.[5] Data,

EVENT WORD (every count)

Bit (starting with high-order bit)

1--- "1"(indicates event word)

2-, 3, 4, 5, 6, 7, 8- : Time-Of-Flight information (0-127)

9-, 10- : detector ring of 1st bank (0-3)

11-, 12- : detector ring of 2nd bank (0-3)

13-, 14, 15, 16- : bank pair (0-8)

17-, 18, 19, 20- : address of detector in 1st bank (0-15)

21-, 22, 23, 24- : address of detector in 2nd bank (0-15)

25-, 26, 27, 28, 29, 30, 31- : wobble point* (0-95)

32--- blank

CONTROL WORD (every wobble point)

Bit (starting with high-order bit)

1--- "0"(indicates control word)

2--- "1" (to prevent EOF bit pattern)

3-, 4, 5, 6, 7, 8- : Z-axis scan information

9-, 10, 11, 12, 13, 14, 15, 16- : Biological gating information

17-, 18, 19, 20, 21, 22, 23, 24- : Detector ring rotation information

25-, 26, 27, 28, 29, 30, 31- : wobble point* (0-95) *(same information as in event word)

32--- blank

Figure 1. Bit pattern of list mode data output by SUPER PETT I system.

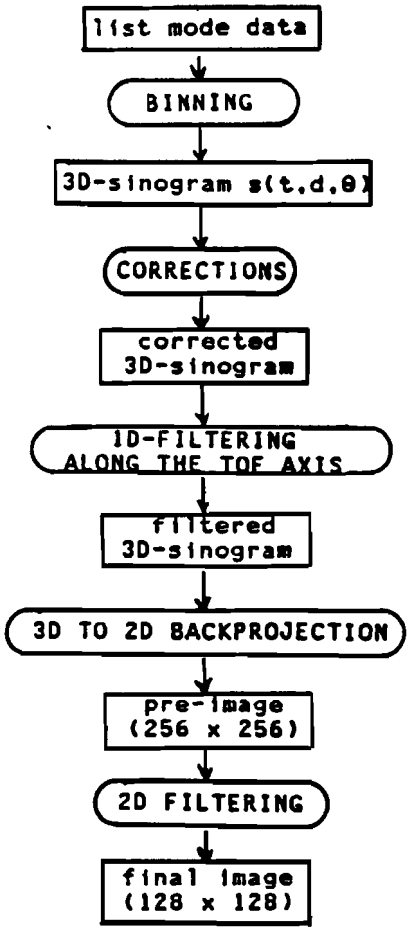

Figure 2. Flow of image reconstruction process with time-of-flight information.

(t,d), belonging to each angle of the filtered 3-D sinogram, (t,d,θ), are superimposed on a pre-image array, (x,y). A circularly symmetric filter, $H_2(R)$, is then applied to the 256 x 256 pre-image array in the frequency domain by using a 2-D FFT method to get the final 128 x 128 image. The optimal filters, $G_1(T)$ and $H_2(R)$, are as follows. When the shape of the point-spread function of the final image is a circularly symmetric Gaussian having a standard deviation of σ_{RESO}, then

$$G_1(T) = \exp[-2\pi^2(\sigma^2_{TOF} - \sigma^2_{BEAM}) \cdot T^2] \quad (1)$$

$$H_2(R) = \exp[+2\pi^2(\sigma^2_{TOF} - \sigma^2_{RESO}) \cdot R^2]/I_0[-2\pi^2(\sigma^2_{TOF} - \sigma^2_{BEAM}) \cdot R^2] \quad (2)$$

where T is the spatial frequency of the TOF information, R is the spatial frequency along distance from the center of the image array, σ_{TOF} is the standard deviation of the TOF information, σ_{BEAM} is the beam width of a detector pair, and $I_0[\ \cdot\ ]$ is a zero-order Bessel function of the first kind.

In the algorithm and the filters, both the TOF measurement error and the beam width are taken into account. This is important not only for optimal imaging, but also for keeping the final resolution exactly the same for images reconstructed with and without TOF.

1. M. M. Ter-Pogossian, D. C. Ficke, M. Yamamoto, and J. T. Hood, Sr., "Design Characteristics and Preliminary Testing of Super PETT I, A Positron Emission Tomograph Utilizing Photon Time-of-Flight Information (TOF PET)," The IEEE Proceedings of the International Workshop on Time-of-Flight Emission Tomography, Washington University, St. Louis, Missouri, May 17-19, 1982, in press.

2. M. Yamamoto, G. R. Hoffman, D. C. Ficke, and M. M. Ter-Pogossian, "Imaging Algorithms and Image Quality in Time-of-Flight Assisted Positron Computed Tomography: SUPER PETT I," The IEEE Proceedings of the International Workshop on Time-of-Flight Emission Tomography, Washington University, St. Louis, Missouri, May 17-19, 1982, in press.

3. D. C. Ficke, D. E. Beecher, G. J. Blaine, R. E. Hitchens, T. J. Holmes, M. M. Ter-Pogossian, and M. Yamamoto, "TOF Acquisition: System Design and Experimental Results," The IEEE Proceedings of the International Workshop on Time-of-Flight Emission Tomography, Washington University, St. Louis, Missouri, May 17-19, 1982, in press.

4. T. J. Holmes, D. L. Snyder, D. C. Ficke, and M. Yamamoto, "Maximum-Likelihood Estimation Applied to Some Calibration Problems in Time-of-Flight Emission Tomography Systems," The IEEE Proceedings of the International Workshop on Time-of-Flight Emission Tomography, Washington University, St. Louis, Missouri, May 17-19, 1982, in press.

5. T. J. Holmes, G. J. Blaine, R. E. Hitchens, and D. C. Ficke, "Implications of Event Rate and Study Parameters on System Architecture," The IEEE Proceedings of the International Workshop on Time-of-Flight Emission Tomography, Washington University, St. Louis, Missouri, May 17-19, 1982, in press.

B-20. Calibration Problems in Time-of-Flight Emission Tomography

Personnel: T. J. Holmes, BCL
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D. L. Snyder, BCL
M. Yamamoto, M.S., Radiology

Support: RR 00396
RR 01380
HL 13851
HL 25944

Emission tomography systems having time-of-flight (TOF) data require calibration before useful reconstructions are feasible. In this study we examine calibration approaches to correct time-of-flight offset and scale-factor errors. Cramer-Rao lower bounds are evaluated as fundamental limits on what can be achieved, and various estimators having performances that approach these bounds for practical system-parameter values are studied. Normalization for detector efficiency, attenuation, and sampling duty-cycle also are studied (B-21).

Our present formulation of a model for TOF offset and scale factor is a first attempt to understand the problem. There are some important additional effects observed in actual TOF data which are not included in the model. One of these is the effect of random-coincidence detection. Because of this we are in the process of formulating a more complete model as a multivariate estimation problem having the offset, scale factor, and random-coincidence count intensity as parameters to be estimated. Initial results were reported at the Time-of-Flight Workshop (B-27).[1]

1. T. J. Holmes, D. S. Snyder, D. C. Ficke, and M. Yamamoto, "Some Calibration Problems in Time-of-Flight Tomography," The IEEE Proceedings of the International Workshop on Time-of-Flight Emission Tomography, Washington University, St. Louis, Missouri, May 17-19, 1982, in press.

B-21. Count Normalization for Conventional and Time-of-Flight Emission Tomography

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Support: RR 00396
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HL 13851
HL 25944

For emission tomography systems which employ detector translation, it is possible for more than one detector pair to be associated with a bin of a conventional projection array. We have found that a composite normalization factor should be applied which combines the efficiencies and sampling duty cycles of all detector pairs associated with a bin. Also, we have determined that this concept of a composite normalization factor cannot be carried one step further into the cells of a two-dimensional pre-image such as the confidence-weighted array of time-of-flight tomography. A maximum-likelihood-estimate approach was used. Our model formulation takes into account only the data collection and pre-image building steps. Future plans are to reformulate the model to include the reconstruction step.

B-22. Simulation of Time-of-Flight Emission Tomography Systems

Personnel: D. G. Politte, BCL
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Support: RR 00396
RR 01380

Simulations of time-of-flight positron emission tomography systems have been undertaken following the mathematical model by Snyder, Thomas and Ter-Pogossian.[1] Two phantoms, a "left ventricle" and a "heart-liver" model, have been imaged. For the latter phantom, the performances of the most-likely position and the confidence-weighted preimage formation schemes were compared. We find that the confidence-weighting scheme leads to superior signal-to-noise performance in the interior of the annulus modeling the left ventricle. For formation of the confidence-weighted preimage array the Gaussian weighting can be carried out over a finite extent, but with some sacrifice in performance. Our results show that updating pixels over three standard deviations of the weighting function on each side of the measured point, for each annihilation, is close to optimum. These results have been reported.[2]

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.

2. D. G. Politte and D. L. Snyder, "A Simulation Study of Design Choices in the Implementation of Time-of-Flight Reconstruction Algorithms," The IEEE Proceedings of the International Workshop on Time-of-Flight Emission Tomography, Washington University, St. Louis, Missouri, May 17-19, 1982, in press.

B-23. Some Noise Comparisons of Data Collection Arrays for Emission Tomography Systems Having Time-of-Flight Measurements

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Support: RR 00396
RR 01380
HL 13851
HL 25944
ENG 76-11565

The noise performance of an emission tomography system having time-of-flight measurements is shown in several examples to be superior for a confidence-weighted data array compared to a most likely position data array. The examples range from a point to a planar distribution of radio-activity, and include a crude model of the left ventricle of a heart containing radio-active palmitate. Results have been reported.[1]

1. D. L. Snyder, "Some Noise Comparisons of Data Collection Arrays for Emission Tomography Systems Having Time-of-Flight Measurements," IEEE Transactions on Nuclear Science, vol. NS-29, no. 1, pp. 1029-1033, February 1982.

B-24. Effects of Quantization of Time-of-Flight Measurements in PETT

Personnel: T. J. Holmes, BCL
D. G. Politte, BCL
D. L. Snyder, BCL

Support: RR 00396
RR 01380
HL 25944

In this study, we are attempting 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. Our analytical results, which are based upon some mathematical approximations, 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 with a "confidence-weighted" pre-image and a time-of-flight measurement error distribution of 6.75 cm FWHM.[1]

We have found that analytical verification of the approximations is non-trivial. Therefore, we will be performing a computer simulation of tomographic data to re-calculate the quantization effects and find the conditions under which our approximations are valid.

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-25. Study of Block-Banded Toeplitz Matrices that Occur in a Time-of-Flight Tomography Algorithm

Personnel: N. C. Cheng, BCL
D. L. Snyder, BCL

Support: RR 00396

In (PR 17, B-15), methods for solving a system of linear equations, characterized by a nonsparable block-banded Toeplitz matrix, associated with a reconstruction algorithm for a most-likely-position array were discussed. The reconstruction algorithm for both the most-likely-position array and the confidence-weighted array are described by similar equations as shown by Snyder, Thomas and Ter-Pogossian,[1] hence similar linear systems can be used to describe the reconstruction algorithm for a discrete, confidence-weighted array, when the matrix entries in the data array are properly identified.

In the limiting case, when the pre-image is infinitely fine, the Fourier transform of the point-spread function associated with the confidence-weighted array and the most likely position array are:[1]

$$G(f)_{CW} = \exp\{-2\pi^2(\sigma_e^2 + \sigma_b^2)f^2\}I_0\{2\pi^2(\sigma_e^2 - \sigma_b^2)f^2\}$$

$$G(f)_{MLP} = \exp\{-\pi^2(\sigma_e^2 + \sigma_b^2)f^2\}I_0\{\pi^2(\sigma_e^2 - \sigma_b^2)f^2\}$$

where σ_e is the standard deviation of the time-of-flight measurement uncertainty, σ_b is the standard deviation of the uncertainty along the direction perpendicular to the coincidence line, and $I_0(\cdot)$ is a modified Bessel-function of the first kind of order zero.

Comparing these two expressions, it is apparent that they are the same except that the standard-deviation parameters differ by a factor of $\sqrt{2}$. In general, they can be represented as:

$$G(f) = \exp\{-\pi^2\sigma_1^2 f^2\}I_0\ (\pi^2\sigma_2^2 f^2).$$

For a confidence-weighted array, $\sigma_1^2 = 2(\sigma_e^2 + \sigma_b^2)$ and $\sigma_2^2 = 2(\sigma_e^2 - \sigma_b^2)$, assuming $\sigma_e \geq \sigma_b$. For a most-likely-position array, $\sigma_1^2 = \sigma_e^2 + \sigma_b^2$ and $\sigma_2^2 = \sigma_e^2 - \sigma_b^2$, assuming $\sigma_e \geq \sigma_b$.

In the case when the uncertainty along the direction perpendicular to the coincidence line is ignored, σ_b equals zero, and σ_1 and σ_2 both equal σ, where σ^2 equals $2\sigma_e^2$ for a confidence-weighted array and σ_e^2 for a most-likely-position array. Then the point-spread function of G(f) becomes: $g(r)=(1/r)(1/\sqrt{2\pi}\sigma)\exp\{-r^2/2\sigma^2\}$. Thus, when the uncertainty along the direction perpendicular to the coincidence line is ignored, the point-spread functions associated with the most-likely-position array and the confidence-weighted array are:

$$g(r)_{MLP} = 1(/r)(1/\sqrt{2\pi}\sigma_e)\ \exp\{-r^2/2\sigma_e^2\},$$

and

$$g(r)_{CW} = (1/r)(1/(\sqrt{2\pi})(\sqrt{2}\sigma_e)\ \exp\{-r^2/2(\sqrt{2}\sigma_e)^2\}.$$

The quantity $a(|i-k|, |j-m|)$ in matrix A (PR 17, B-15) is the discrete version of the continuous, point-spread function of a most-likely-position array convolved with a pixel function. Let $q^2 = (i-k)^2 + (j-m)^2$, and, for $(i,j) \neq (k,m)$, define the quantities

$$\tilde{g}(|i-k|,\ |j-m|) = \sin^{-1}(1/\sqrt{\pi}q),$$

$$\bar{z}_{km}=(\delta/\sqrt{\pi})/\tilde{g}(|i-k|,\ |j-m|),$$

$$\Delta\bar{z}_{km}=(\delta/4q)/\tilde{g}(|i-k|,\ |j-m|),$$

and

$$f(|i-k|,\ |j-m|)$$
$$= \Phi\{(\delta/\sigma)/\sqrt{\pi}\tilde{g}(|i-k|,\ |j-m|),((\delta/\sigma)/4q\tilde{g}(|i-k|,\ |j-m|)\},$$

where:

$$\Phi(z/\sigma,\ \Delta z/\sigma) = \int_{(z-\Delta z)/\sigma}^{(z+\Delta z)/\sigma} (1/\sqrt{2\pi})\exp\{y^2/2\}dy,$$

and

$$g(|i-k|,\ |j-m|)=(2/\pi)\ \tilde{g}(|i-k|,\ |j-m|).$$

Then

$$a(|i-k|,\ |j-m|) = g(|i-k|,\ |j-m|)f(|i-k|,\ |j-m|)(\sigma/\delta).$$

When (i,j) equals (k,m):

$$a(0,0) = \Phi(0,r_0/\sigma),$$

where $r_0 = \delta/\sqrt{\pi}$.

The point-spread function of a confidence-weighted array differs from the point-spread function of a most-likely-position array only by a factor in the parameter σ_e. When σ in the definition of $a(|i-k|,\ |j-m|)$ is replaced by $\sqrt{2}\sigma_e$, the resulting matrix represents a discrete version of the point-spread function of a confidence-weighted array. To summarize, the reconstruction algorithm for a most-likely-position array is:

$$A_{MLP}\ \hat{\underline{S}} = \underline{n}_{MLP}/N_t,$$

where $\underline{n}_{MLP}$ is a discrete version for the most-likely-position array, and

$$[A_{MLP}](i,k;j,m) = g(|i-k|,|j-m|)f(|i-k|,|j-m|)(\sigma/\delta).$$

The reconstruction algorithm for a confidence-weighted array is:

$$A_{CW}\ \hat{\underline{S}} = \underline{n}_{CW}/N_t,$$

where $\underline{n}_{CW}$ is a discrete version of a confidence-weighted array, and

$$[A_{CW}](i,k;j,m) = g(|i-k|,|j-m|)f(|i-k|,|j-m|)(\sqrt{2}\sigma/\delta).$$

The matrices A_{MLP} and A_{CW} are both non-separable block-banded Toeplitz-matrices, so the method developed in (PR 17, B-15) applies to a confidence-weighted array as well as a most-likely-position array.

1. D. L. Snyder, L. J. Thomas, 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-26. Studies of Detector Electronics for Time-of-Flight Tomography Systems

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Support: RR 00396
RR 01380
HL 25944

In positron-emission tomography utilizing time-of-flight information, one of the important system parameters is the uncertainty associated with the time-of-flight measurement. Several factors contribute to this uncertainty, including the length of the scintillation crystal, its absorption and emission characteristics, and the time jitter associated with the photomultiplier tube.

A study[1] has shown that in scintillators that are typically used, the length of the crystal should have a negligible effect on the measured time uncertainty. This does not agree with experimental evidence, possibly because the study did not include self absorption of photons liberated in the crystal. Further work is needed to clarify this point.

Photomultiplier time-jitter appears to be the main source of time uncertainty. Micro-channel-plate photomultipliers show promise of reducing the jitter by at least a factor of two, and so work is underway at BCL to measure their performance. Of particular interest is the improvement in time jitter that can be expected using a reputedly faster scintillator, barium fluoride. Two micro-channel-plate devices, modified for the emission characteristics of barium fluoride, are being acquired for this work. To avoid the saturation effect inherent in presently available micro-channel-plate photomultipliers will require that the photomultiplier be followed by an amplifier. The amplifier will need to have about 40 db gain and 300 mHz bandwidth and several designs are under investigation.

1. R. Gregory, "Some Limitations of Time-of-Flight Detectors," The IEEE Proceedings of the International Workshop on Time-of-Flight Emission Tomography, Washington University, St. Louis, Missouri, May 17-19, 1982, in press.

B-27. International Workshop on Time-of-Flight Emission Tomography

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G. J. Blaine, BCL
J. R. Cox, Jr., BCL
S. A. Gonzalez-Rubio, BCL
M. E. Harbison, Computer Science
M. E. Raichle, M.D., Neurology and Radiology
D. L. Snyder, BCL
M. M. Ter-Pogossian, Ph.D., Radiology

Support: RR 01358
RR 01380
IEEE Computer Society
Hamamatsu Corporation
Nucletronix and Scanditronix
Washington University

The near completion of several prototype systems for utilizing time-of-flight information in positron-emission tomography plus recent developments in reconstruction algorithms, photon-detection devices, and system architectures stimulated us to convene an international workshop at the Washington University School of Medicine, May 17-19, 1982. Approximately 60 participants from France, Japan, and the United States represented the disciplines of biomedicine, mathematics, physics, electronic engineering, and computer science from universities, independent research facilities, and commercial firms.

Five scientific sessions addressed biomedical motivations, systems under development, event detection, reconstruction algorithms, and design considerations for data acquisition and processing. Each session included formal presentations followed by an ample period for participant interactions directed by discussion leaders. Following a demonstration of SUPER PETT I in the Division of Radiation Sciences, a concluding plenary session was held to review and approve summary reports prepared by the chairmen and discussion leaders of their respective scientific sessions. Presented papers and the summary reports will be published as a Proceedings by the IEEE Computer Society.

The workshop provided an especially useful forum for conveying the needs of biomedical users to system designers and for emphasizing the implications of the strengths and weaknesses of time-of-flight emission tomography for biomedical applications. A major highlight that had impact on all of the sessions was the announcement of a new fast (0.8 nsec decay constant) scintillator, BaF2, by the group from Centre d'Etudes Nucleaires de Grenoble. The rate of light emission is about a factor of two better than CsF, and BaF_2 is not hygroscopic as is CsF. Early results from SUPER PETT I were presented to show that the improvement in signal-to-noise ratio due to the use of time-of-flight information meets or exceeds that predicted theoretically for reconstructions based on confidence-weighted arrays.

C. Systems for Specialized Biomedical Studies

Projects in this section encompass a wide range of clinical and basic disciplines; emphasis is on acquisition and manipulation of physiologic data.

Perhaps the most significant work is the study of the yeast genome by photo-electric imaging and subsequent computer processing. The complexity of genetic systems is such that an attack on any but the most rudimentary organisms mandates the use of robust automated procedures.

Progress continues to be made in the development of automatic methods for autoradiography. The silver-grain counter is operational and its algorithms are being tested and improved.

In the area of visual studies the "rigidity" of the eye is being examined and there has also been substantial progress in the study of three dimensional visual fields which are of value in defining the extent of degenerative changes concomitant on early glaucoma. Also related to the detection of glaucoma, color perimetry methods are in an advanced state of development.

A data acquisition scheme for the study of canine coronary occlusion is in regular use in the Jewish Hospital. In the light of operating experience and in view of the need for longer data sets, the system's data storage capacity is being increased.

The specialized EEG display system has been used on volunteer subjects and protocols for a normative EEG study are under way. It has been found necessary to elaborate certain parts of the processing system and to devise methods, unexpectedly complicated, for stimulus presentation.

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

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J. L. Price, Ph.D., Anatomy

Support: RR 00396
RR 01380
NS 15070

The motivation behind and the development process of a second generation automated system for high-speed quantification of neuroanatomical autoradiographs has been described in several previous reports (PR 15, F-4; PR 16, F-4; PR 17, C-1). Work in the past year has centered primarily on refinements to and documentation of the instrument's hardware and software. A performance evaluation more extensive than that previously reported was conducted in an attempt to quantify the accuracy with which the machine counts the number of silver grains in an autoradiograph. In addition, a number of new utility programs were written to assist in the maintenance and evaluation of the system. Finally, the system was utilized to obtain digitized images of autoradiographs for use in data compression studies (E-11).

The most important refinement of the system's algorithms and software was the installation of the "shrink" grain counting algorithm. The original grain counting algorithm, called the "endpoint" detector, attempts to locate the lower left corner of each silver grain. The endpoint algorithm is simple, very fast, but has a tendency to begin missing grains when the tissue specimen is very heavily labeled, and thus the autoradiograph's silver grains are closely packed. The shrink algorithm reduces each isolated cluster of above-threshold pixels to a single pixel, and then counts the number of isolated pixels remaining. Although more complex and slower than the endpoint detector, the shrink algorithm is much more accurate when dealing with dense autoradiographs.

A modest detector performance evaluation was conducted in November 1981 to assess the machine's count accuracy compared with a panel of four experienced human reviewers. A test data set of eight widely different autoradiographs was selected by an experienced neuroanatomist. Each of the eight images was then analyzed by the human reviewers and the grain counter utilizing both the endpoint and shrink algorithms. The results of the test were encouraging, with the machine counts differing from the average human count by 7.7% and 2.5% for endpoint and shrink algorithms respectively. In general, the machine tended to underestimate the number of grains present, since it was usually unable to deduce the presence of two or more overlapping grains when it encountered large, irregularly shaped clusters in the image.

During the past year the specialized imaging subsystems of the grain counter also have been used in a number of image processing experiments, ranging from digitizing cells undergoing division, to the study of the retinas of diabetic patients. The architecture of the system has proven to be quite flexible.

C-2. DNA Restriction Mapping Studies

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Support: RR 00396
RR 01380
GM 28232

Constructing a complete physical map of the yeast genome will require the preparation and analysis of hundreds of electrophoretic gels. The rationale for and background of this project has been previously reported (PR 16, G-10; PR 17, C-2). During the preceding year considerable progress has been made in fabricating a semi-automated system for the extraction of DNA fragment size data from these electrophoretic gels utilizing a solid-state image digitizer (Eikonix EC 78/99), a Digital Equipment Corporation LSI 11/23, and a Lexidata 3400 raster display system. A block diagram of the hardware configuration is shown in Figure 1.

The Eikonix EC 78/99 was selected based upon experiments which showed that an imaging device with at least 1024 pixels down each "lane" of a gel was necessary to reliably resolve closely spaced bands. Conventional drum-type densitometers and vidicon-tube imagers were rejected; the former because of low speed, high cost, and inflexible specimen format, and the latter due to limited resolution, and rigid readout requirements. The Eikonix EC 78/99 consists of a linear array of 2048 photodiodes and a precision stage for translation of the linear array across the field of view. The EC 78/99 produces a raster of 2048 × 2048 × 8 (or 12) bits of data. Data readout format is exceptionally flexible. The EC 78/99 also provides a suitably uniform light source for illumination of the image media, as well as computer control over illumination level, integration time and other imaging parameters.

Display of image data, results, and interactive editing of fragment size data are facilitated by the Lexidata 3400 display system. The configuration selected for this project produces a 640 × 512 × 8 bit color image on a high-resolution, long persistence phosphor monitor.

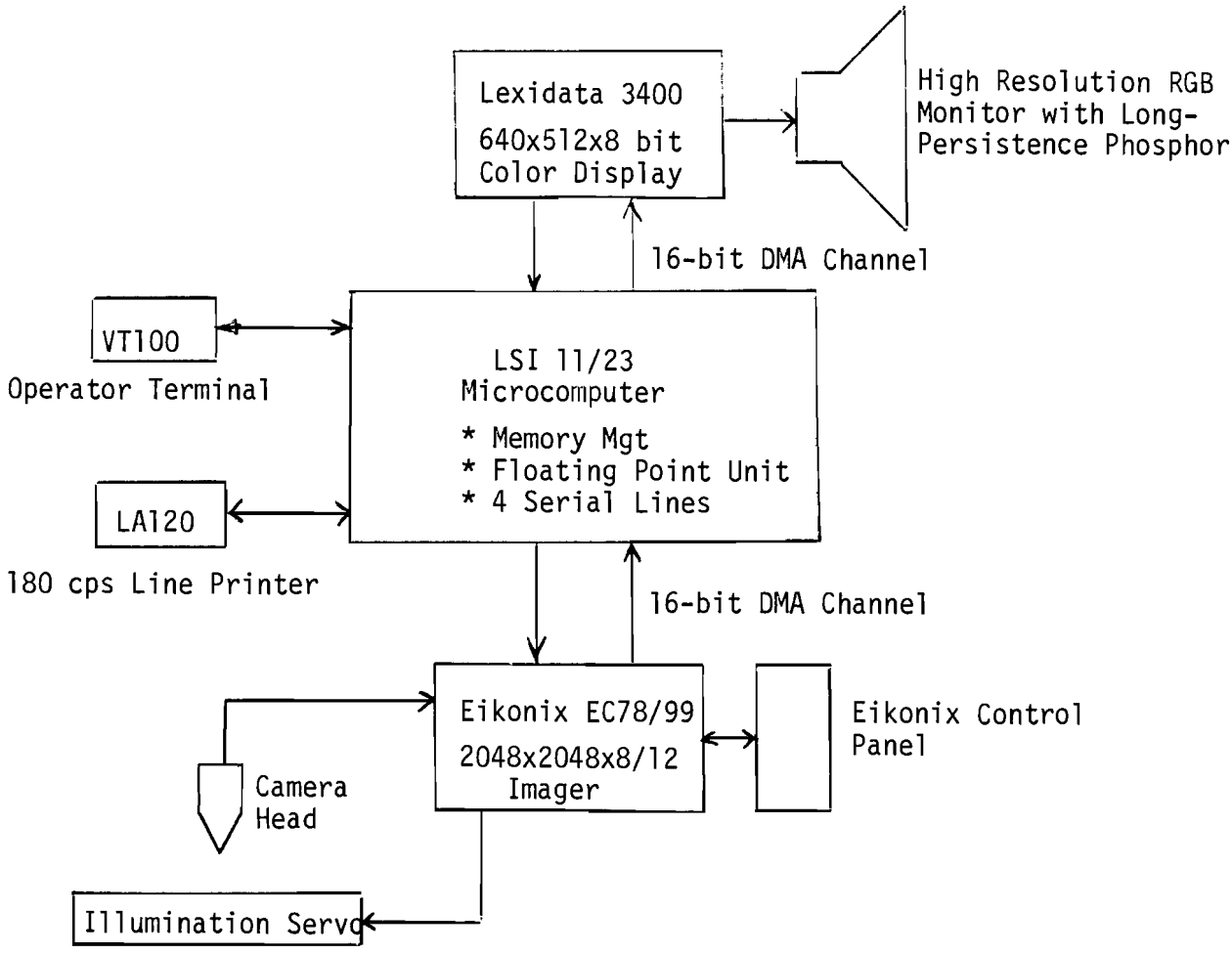

Figure 1. Block Diagram of a DNA Mapping System Hardware Configuration

The hardware of the gel reading system is nearly complete. Work is currently underway on the design and implementation of the data acquisition and analysis software. The initial version of the software will be designed and implemented as a series of subsystems, which may be independently chained via a small, menu-driven monitor program written under RT-11. At this writing, three distinct subsystems have been identified and partially designed; implementation has been started on one. The three subsystems are Creation, Gel Reading, and Update & Review.

Creation allows the user to create a new datafile and enter all header information pertinent to the new gel. This subsystem has been designed and partially implemented.

Gel Reading will scan an entire gel via the Eikonix Digitizing system and store all relevant information extracted into the datafile created via the Creation subsystem. This subsystem has been partially designed.

Update & Review will allow the user to retrieve, examine, and change any portion of a previously created data file. This subsystem has been partially designed.

These modular software subsystems, each of which can be operated independently given a data file, offer much flexibility to the overall software system. The major advantage of this approach is that each subsystem can be designed, implemented, and most importantly, debugged independently of other subsystems. This methodology is useful not only during initial system development, but also when future issues of maintenance, enhancement, and modification are considered.

In the previous progress report (PR 17, C-2), it was indicated that a probabilistic model of DNA base pairs was developed to aid in the reconstruction of the genome from the experimental clone data. To test the validity of the proposed model, a data set of 100 clone samples was prepared by Dr. Olson. This data set was completed at the end of the progress report period. We propose to use this data set to verify that the lengths of the DNA fragments are exponentially distributed and independent of each other. We propose to use the samples to develop a model for errors in measuring the lengths of the fragments. This error model will be a key step in developing a sequential procedure for reconstructing the genome. We also propose to study the feasibility of using partial digestion techniques to obtain both order and length information about the fragments in each clone.

C-3. Ocular Rigidity Measured by Applanation Tonometry

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Support: RR 00396
EY 00256
EY 02687

A mathematical description of the dynamic pressure-volume behavior of the eye is called ocular rigidity. This function has been investigated repeatedly during the last century and many formulations have been proposed.

A versatile programmable applanation tonometer described earlier[1] provides data from the initial ramp application of force to the tonometer which could be assembled into a pressure-volume curve, and a pressure-volume function was derived. This function showed the eye to be more distensible than found previously by other methods. The effect of this method of ocular rigidity measurement on the results has been discussed.[2]

1. R. A. Moses, W. J. Grodzki, and R. J. Arnzen, "Constant Area Applanation Tonometry," Investigative Ophthalmology and Visual Science, vol. 20, pp. 722-725, 1981.

2. R. A. Moses and W. J. Grodzki, "Ocular Rigidity by Applanation Methods," Medizin and Naturwissenschaften, in press.

C-4. Visual Fields and Ocular Hypertension

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R. W. Hagen, BCL
L. J. Thomas, Jr., BCL

Support: RR 00396
RR 01380
EY 02044

During the past year work was completed on the development of three-dimensional static perimetry using the modified Goldmann perimeter with an M6800-based microprocessor recording device. Initial results of examining a variety of patients with this instrument were reported, demonstrating the clinical utility of three-dimensional static perimetry.[1]

During the same period of time work was completed on bringing up-to-date the visual fields database of a population of approximately 1,000 patients with ocular hypertension and/or known or suspected glaucoma. Using the previously developed techniques of automated pattern analysis and three-dimensional static perimetry, a retrospective chronologic analysis of the course of onset and evolution of glaucomatous visual field defects was undertaken.[2] Evidence was accumulated to demonstrate that the onset of glaucomatous defects is an insidious process, the very earliest stages of which are characterized by transiently appearing, shallow defects within the visual field. The subsequent course of the disease is characterized by dense non-transient defects that seem to progress inexorably to produce extensive loss of vision within one decade in spite of the best medical and surgical therapy available.

Future work on this project will involve the use of three-dimensional static perimetry, confined to selected areas of the visual field, in an attempt to improve the reliability of early diagnosis of disease prior to the stage at which visual field defects become permanent and progressive.

1. W. M. Hart, Jr. and R. K. Hartz, "Computer-Generated Display for Three-Dimensional Static Perimetry," Archives of Ophthalmology, vol. 100, pp. 312-318, 1982.

2. W. M. Hart, Jr. and B. Becker, "The Onset and Evolution of Glaucomatous Visual Field Defects," Ophthalmology, vol. 89, pp. 268-279, 1982.

C-5. Color Perimetry Studies

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B. J. Bigner, Electrical Engineering
R. W. Hagen, BCL

Support: RR 00396
RR 01380
EY 02044
EY 03703

This project involves the design of a microprocessor-controlled video display device to present visual stimuli for the testing of the visual field, using color-specific test objects. For this purpose the test objects to be used are to be psychophysically matched to their surrounds in terms of luminance, such that they represent pure color-contrast targets. A video display generator has been constructed which allows generation of images

on a 19 inch Raster scan color television monitor of targets of square or oblong shape of any size to be positioned anywhere on the screen; and to be independently controlled for brightness for each of the three phosphorus (red, green and blue).

Using heterochromatic flicker photometry it has been possible to luminance-match colored targets to achromatic (gray) surrounds, and then to subsequently vary the color saturation of targets to explore visual thresholds that represent an isolated chromatic function.

The video display device, along with a calibrating photometer, communicate with a Motorola Exorset control unit by way of an IEEE 488 bus.

During the coming year a stylus-controlled graphics tablet will be added to this system to allow interactive control of target position, brightness and color properties. When complete, this system will allow examination of the central visual field with targets that specifically test an isolated color function. The clinical importance of such a device lies in the theoretical expectation that visual field defects produced by glaucoma in its very earliest stages should be more pronounced and more easily detected as defects for color perception, prior to the appearance of defects which are mapped by conventional techniques of brightness threshold.

1. W. M. Hart, Jr., "A Theoretical Foundation for Color Perimetry," presented at the Association for Research in Vision and Ophthalmology Meeting, Sarasota, Florida, May 3, 1982.

C-6. Data Acquisition System for Extracellular Cardiac Potentials

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Support: RR 00396
RR 01380
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The use of this data acquisition system (PR 17, C-6) has continued in studying the effects of coronary occlusions on canine electrograms. Studies examining the combined effect of autonomic nerve activity and coronary occlusions have been started. The software has been enhanced to include a program which summarizes the results of electrogram analysis on a graphics terminal and the results of a complete experiment can now be stored on a

single LINCtape. Work has begun on a program which transfers these results to industry-compatible nine-track tape. This tape will provide a convenient medium for transferring electrogram information to another system for statistical analyses.

Though the acquisition system has been used for short-term acute experiments, a need in this research work is to conduct similar long-term experiments. The signal-to-noise ratio and frequency domain properties of the electrogram signals, acquired during acute experiments, have been determined to aid in identifying the acquisition and storage needs for long-term experiments. These signals demonstrate that the quantizing resolution of an 8 bit converter is sufficient to maintain the physiologic signal-to-noise ratio during short-term experiments. However, long-term experiments can benefit from the use of a higher resolution A/D converter. The frequency domain analysis shows that 99.9 percent of the electrogram energy is contained at frequencies below 550 Hertz. A properly filtered electrogram sampled at 2000 samples per second should satisfy the electrogram acquisition requirements for long-term experiments. Several data compression schemes were compared and some implementation tradeoffs were described.[1]

1. B. H. Tanaka, "System Design Considerations for Acquisition of Canine Cardiac Electrograms," Master of Science thesis, Department of Electrical Engineering, Washington University, St. Louis, Missouri, December 1981.

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

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Construction of the prototype 9-channel unit was completed in the Fall of 1981 and a technical description was prepared and published.[1] Preliminary recordings were made on a number of volunteer subjects using the Barnes Hospital evoked-response laboratory through the courtesy of Dr. Lawrence Coben. These confirmed some of the observations of Walter and Shipton.

Two technical problems were encountered during these experiments: one involves the phasing of external stimuli and this has not yet been satisfactorily resolved. The second problem is a consequence of the superior resolution of the display. There have been tantalizing glimpses of very small phase shifts in alpha rhythms; if these are to be studied in detail, an improved data acquisition scheme will be needed. Present work is concentrated on this aspect of the system. If the memory size is increased,

an increase in complexity is inevitable and while this may not be important in the present 9-channel device it will become significant if a proposed 24-channel instrument is constructed. If, on the other hand, the sample time is reduced, then some operational convenience is sacrificed.

Requests for reprints of the technical description have been heavy and at least two EEG groups are considering duplicating the system. The possible uses of the system were discussed with Dr. R. Cooper of the Burden Neurological Institute (where the original toposcope was developed) and the possibility of joint experiments is under consideration.

1. H. W. Shipton and G. L. Armstrong, "A Modern Frequency and Phase Indicating Toposcope," Electroencephalography and Clinical Neurophysiology, vol. 52, pp. 659-662, 1981.

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/370 based resources. 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). This model is being implemented in the programming language C. The specification of the Neonatology Database (D-2) in ADS will provide one mechanism to evaluate the model and its implementation. 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.

Economic constraints have caused changes in the operation of several databases. The Neonatology Database remains accessible but has been placed on tape because funds were unavailable to continue its on-line operation. The Mineral-Homeostasis and Mineralization Database and Obstetrics Database are supported by their users. Each division performs its own data management and pays for appropriate computer services.

D-1. Information Systems Group

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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 useful to 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 to include abstraction on symbols as a primitive concept. ADS is believed to be an appropriate model of sufficient power to allow translation between other existing data models. A database design aid has been implemented in MUMPS which provides an environment for the construction of an ADS description of the Neonatology Database. Design studies of pattern-matching architectures suited to VLSI implementation have continued.[1] Our initial

experiment, a serial-register associative memory, resulted in two functional chips which were tested to compare predicted to actual performance.[2]

Implementation activities include developing an ADS system in the C programming language on a PDP-11/34 computer. Software is being developed to facilitate transport of the C-based implementation to a Motorola 68000 (M68K) experimental configuration. Specific details of these activities are summarized elsewhere.[3]

1. S. Moore, J. Blaine, M. Browder, R. Hitchens, and J. R. Cox, Jr., "Study of a Systolic Array Used in an Associative Memory," Information Systems Group Working Note 40, July 1982.

2. S. Moore, J. Blaine, M. Browder, R. Hitchens, and J. R. Cox, Jr., "Test Results from VLSI Trial Design," Information Systems Group Working Note 39, July 1982.

3. "A Medical Information Systems Design Methodology," HS 03792-04 Continuation Application, J. R. Cox, Jr., June 1982.

D-2. Neonatology Database

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The Neonatology Database (PR 17, D-2) was designed to allow the easy formulation of queries by medical personnel and to provide a rapid response to such queries. In the current year the enrollment of patients has ceased and the entire database has been placed on tape for use in Information System Group studies (D-1). The database's advocate, Dr. Michael Maurer, has become Director of the Special Care Nursery at St. John's Mercy Medical Center in St. Louis, Mo. and sufficient funding was unavailable at Children's Hospital to continue the project. The database was documented in detail before it was placed on tape. Rush-Presbyterian-St. Luke's Medical Center of Chicago is basing their development of a neonatal database on the Neonatology Database (NDB) and St. John's Mercy Medical Center has also expressed an interest in the database.

The NDB has provided a convenient mechanism for medical personnel to pose questions based on historical, clinical, and/or laboratory data which arose as they dealt with sick infants. Admission data, including maternal history, perinatal history, immediate post-delivery data, and initial admission evaluation were gathered soon after an infant's admission. Disposition data were gathered at appropriate times during the hospitalization. A research nurse summarized the in-hospital stay by recording problems, therapies, and procedures along with related complications, concurrent events, attributes, and features.

At different times, this MUMPS-based database has existed on three separate computer systems since its inception in June 1975. The database was developed as a pilot study on an Artronix PC-1200 system. When it matured, the database was transferred 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. The database was stored on tape in May, 1982. At that time, the patient population was 2728.

The NDB matured into a useful tool. A response to typical queries was made in seconds because bit functions were utilized with the inverted files. Queries involving temporal relationships were answered in one to two minutes. The query-specification method allowed a user to respond to a series of prompts by keying only enough of the desired term to avoid ambiguities. Data integrity received considerable attention in this application. Consistency checks were applied during data keying and then data items were compared in a batch mode after all items in a class were entered. Two other databases were developed by utilizing the system's generalized format: Mineral-Homeostasis and Mineralization Database (D-3) and Obstetrics Database (D-4). Changing the data-collection method from retrospective to online is viewed as the next step in the evolution of this database. This enhancement would encourage increased use of the clinical database and improve data quality. A detailed data dictionary and list of consistency checks exist as an important first step in this process.

The NDB will continue to provide an important frame of reference for the development of the data model called Abstract Database System (ADS). In the current year, a design aid for ADS was developed in MUMPS so a detailed specification of the NDB in ADS could be made in parallel with the development of the ADS system in the programming language C. The design aid provides a convenient mechanism to organize and edit an ADS program. It does immediate or delayed syntax checking and some semantic checking. Ad hoc MUMPS programs can be written to analyze the evolving information structure. Currently, the specification consists of 800 ADS commands which define the coding catalogs, the patient files, tracking of the data-collection process, consistency checks, and queries based on the coding catalogs. Items still to be specified include the search dictionary, sorting and printing, time-based queries, and quantitative

data. When development of the ADS system is complete, the NDB specification from the design aid can be executed and evaluated.

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-Homeostasis 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 270 infants have been studied on a series of feeding regiments to evaluate vitamin D metabolism, general growth, bone mineralization, and calcium-phosphorous homeostasis.

Infants are studied serially at three-week intervals with X-rays and chemistries. Intakes and weights are recorded daily and lengths and head circumferences are recorded weekly. Prenatal, maternal, neonatal, and hospital-course data are collected as well. The infants are followed in a special clinic where long-term follow-up data, including growth parameters, I.Q. testing, and dental evaluations are collected. All of these data are gathered and entered by a Pediatric Nurse Practitioner.

This database is used extensively to analyze quantitative data in a variety of time frames. The portion of the system which deals with quantitative data was redone in the current year in order to increase the variety of time frames which could be specified by a user and also to make other needed changes. The selection of quantitative data was organized into one routine which is used by a variety of programs so enhancements to programs dealing with quantitative data could be made easier. A feature was added to allow a user to define search subsets based on quantitative data.

This database will aid the development of the ADS data model because of its emphasis on quantitative data, because of the weekly 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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The Obstetrics Database utilizes the generalized format provided by the Neonatology Database (D-2) and contains data on all deliveries performed at Barnes Hospital since March 15, 1981 and performed at Jewish Hospital since July 24, 1981. Data forms which are included in the patient's hospital chart are completed by the appropriate resident. These forms are reviewed by a physician or nurse, 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-seven questions are answered per mother and an additional twenty-six questions are answered for each birth.

This database, which now includes 6448 patients, is of interest for a number of reasons:

1) The Neonatology Database, Mineral-Homeostasis and Mineralization Database, and this database have similar information and in some cases a patient appears in more than one database.

2) The same data represent two views, i.e., mother and infant due to the possibility of multiple births.

3) This is the first database which was established with consistency checking included at its inception.

4) Data are collected by house staff rather than special research nurses.

The database has served as a good test bed to evaluate the effectiveness of detailed consistency checking. At first, the obstetrician in charge of the database reviewed all forms before their entry into the computer system. In addition, all potential problems identified by the consistency checks were brought to his attention. Because of the consistency checks, modifications were made to both patient data and to the consistency checks. This duty is now performed by a nurse at Barnes Hospital and an obstetrician at Jewish Hospital. The data-entry form is being redesigned so portions

of it will be completed by a staff nurse. The resident physicians will complete the remaining part of the form. It is hoped that this new strategy will improve data quality further.

A special research database on mothers who suffer pre-term rupture of their membrane has also been defined. There are 425 mothers registered in the system. 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. These data were used recently to determine if the use of steroids in mothers who have pre-term rupture of the membrane reduces the incidence of moderate or severe respiratory distress syndrome in the infant. Although the analysis revealed some interesting data, it could not be determined whether the extremely small infant, under 30 weeks gestation, will derive benefit from this therapy. These data as well as two other studies suggest that there is a benefit, but a definitive conclusion must await additional patient evaluations.

D-5. SCOR Patient Information Database

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The Specialized Center for Research (SCOR) database (PR 17, D-5) currently contains information pertinent to 602 patients who suffered acute myocardial infarction (AMI) and 350 patients followed to observe the incidence of early recurrent infarction (ERI). The variables contained in the AMI database describe the patient's 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 into the Interdata 7/16 computer system in the coronary care unit (CCU) and then transferred via magnetic tape to the IBM System/370 at the University's Computing Facilities. There, a permanent SAS database is maintained in order to address a variety of clinical questions. The ERI database contains information which is considered to have a significant bearing on the occurrence of repeat infarctions during the patient's stay in the CCU. These data are stored in a SAS database.

The AMI database was used to identify factors contributing to the known low survival of diabetics with myocardial infarction (MI). Infarct size, the incidence of congestive heart failure (CHF), and survival were assessed in 68 diabetics and 335 non-diabetics with MI. Infarct size was significantly less in diabetics than in non-diabetics ($p<.02$), but CHF occurred more often ($p<.003$). The Mantel Cox test yielded lower survival in diabetics than in controls ($p<.04$).

The patient population in the ERI database demonstrated a high incidence (42%) of early recurrent infarction after initial subendocardial infarction. Stepwise logistic regression identified four significant descriptors (subendocardial locus, recurrent chest pain, female gender and obesity) as having potential value in the prediction of ERI. In order to test the value of these four descriptors, the regression coefficients which resulted from this analysis were applied prospectively to a new population consisting of 134 patients. The presence or absence of ERI was predicted correctly in 82% of the patients (23/28) with ERI and 79% without ERI (84/106). Since it is possible to predict with a high degree of accuracy those patients who will suffer an ERI, the efficacy of prophylactic interventions can be assessed.

E. Supporting Activities

Supporting activities are those 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 expertise of the BCL staff and the inventory of computing and specialized test equipment. Service to users does not follow the usual computation-center pattern with an established fee schedule and a highly centralized facility. Rather, senior laboratory staff members consider requests for assistance from investigators who must address a particular biomedical computing problem. If an appropriate technology exists, investigators may be referred to commercial vendors or fee-for-service organizations when these are available. In other cases, problems may be approached by the laboratory provided that the effort complements other activities of the laboratory. Many times the project can be assigned to a staff member with appropriate experience and completed in a short time. The investigator then has his or her results, and a short note describing the work will appear in the annual report and perhaps the open literature. A few projects, however, may develop into major initiatives within the laboratory. Most of the major projects began in this fashion and the opportunities that supporting activities provide are valued.

The broad spectrum of projects reported on in this section may be categorized as biomedical applications, system development aids, digital hardware designs, and ad hoc studies. The biomedical applications represent new initiatives in which basic explorations are being conducted, some having potential for becoming major, long term programs. An example is the DNA restriction mapping work which was previously reported in this section, but which has matured to the point where it is reported under Systems for Specialized Biomedical Studies (C-2). Even when an extended collaboration does not develop, the relationships cultivated and the experiences gained frequently prove beneficial to future work.

System development aids primarily benefit BCL staff, but may also be used by others. Examples include microprocessor development support and RSX-11 system enhancements. System software developments reported here also are widely utilized in a variety of projects.

Many digital hardware designs are one-time, special purpose projects. The implementation of an apparatus control unit for use in retinal studies (E-15) is an example. Others may have wide appeal and construction of multiple copies is envisioned, an example being the TERRANET local network.

The topics of the studies reported in this section are quite varied. Some are theoretical and address a highly specific problem; others are more properly thought of as feasibility studies.

E-1. Microprocessor Development Support

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HS 03792

In the past year, considerable effort has been expended on the completion of hardware and software support facilities for development of systems based on the Motorola M68000 (M68K) 16-bit microprocessor. Assembly language as well as high-level language software development is available on a variety of machines throughout the Washington University Computer Laboratories (WUCL). Hardware development is centered around the General Radio model 2300 development system and in-circuit emulator.

Early last year a task force consisting of personnel from BCL, CSL, and CS was formed to upgrade a Version 6 UNIX (a trademark of Bell Laboratories) system to Version 7. One of the main reasons for this work was the availability from the Massachusetts Institute of Technology (MIT) of a C language cross compilation system. This system contains a C compiler, an assembler, a linkage editor, and various other utilities for cross compiling C programs from a host computer to an M68K processor. The MIT facility has been installed on a DEC PDP-11/34 and has been augmented with downloading programs and a disassembler. The installation of this system and the installation of TERRANET (E-8) has given us a widely available, sophisticated development support facility for M68K based systems.

Evaluation of several general-purpose prom programmers is currently underway. The acquisition of a commercially available programmer which can be interfaced directly to development support processors, will provide support for a variety of programmable devices.

Software and hardware development support for 8-bit microprocessors continues to be supported by FORTRAN-based cross-assemblers (FOCRAS) and intelligent consoles (Inc). Support for bit-slice processors based on the AMD 2900 series components is supported with an Advanced Micro Computers System 29 development system (PR 17, F-1).

E-2. PDP-11/34 Hardware Support

Personnel: R. E. Hitchens, BCL
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RR 01380

Several changes have been made to the PDP-11/34 systems previously reported (PR 17, F-2) in order to provide improved and more coherent computing support.

The real-time, graphics and image processing 11/34 system has been upgraded to support RSX-11M through the addition of an 80 Mbyte disk system. Other features of this system remain unchanged.

The existing RSX-11M 11/34 system has an additional 5 Mbyte of RK-05 equivalent disks and an additional 800 BPI tape drive. There are now two ports into the TERRANET local area network (E-8). Dial-in modem support with automatic 300/1200 baud line switching has been added. These communication lines are also shared with two local printing terminals. Future plans include a UNIBUS to LSI-11 bus adapter and LSI-11 backplane. This will allow low cost LSI-11 peripherals to be installed. Initially, a DZV-11 four-line asynchronous multiplexer will be added to provide improved network protocol and modem support.

E-3. RSX-11M System Support and Expansion

Personnel: R. E. Hermes, BCL
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RR 01380

The support provided by the RSX-11M (a product of Digital Equipment Corporation) multi-user operating system to the local user community has continued to grow at a steady pace. The system is used primarily for its text editing capabilities which are supported by three different text editors. FORTRAN is the most commonly used programming language, usually used in conjunction with the FORTRAN preprocessor RATFOR. In addition, the system supports LISP, PASCAL, and a C compiler. Other software support includes RUNOFF for text formatting and VERSAPLOT (supplied by Versatec) for plotting as well as other graphics needs.

The system is frequently used to run computationally bound tasks which often require large amounts of disk storage. These tasks which usually involve

some aspects of signal processing or stochastic modeling may run for periods of a few hours to several days or weeks without intervention. Other programs are written and debugged using the facilities of this system and then transferred for use on other stand-alone systems with limited system resources.

The expansion of the system hardware to support nine terminal ports and the addition of the local network TERRANET (E-8) has greatly improved system availability. A second PDP 11/34, also running RSX, is used to support a Lexidata raster-scan graphics system.

Significant software additions, both system and user application programs, have been made to the system largely due to the availability of free software from DECUS, an organization of DEC system users. Within the DECUS organization, is a special interest group for RSX users from which software is acquired and then distributed freely to all interested members.

E-4. Software Support for Image Processing and Display

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Support: RR 00396
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HS 03792

Plans for development of the ADS data model by the Information Systems Group (D-1) include the use of the Lexidata 3400 raster-scan image and graphics processor. To support this effort, a driver was installed in the version 7 UNIX system operating on a PDP 11/34. FORTRAN callable graphics, image and text routines were written to be compatible with routines already available under RT-11 and RSX-11M. The same routines were modified and incorporated into a separate library file for use with programs written in C.

A higher level language for manipulating vector-based images on the Lexidata system is under development. The language, called GRAFIC, will provide the ability to quickly create and update images by combining some of the currently used low-level primitives to form more powerful operators in a PASCAL-like language. GRAFIC is being implemented as an interpreter in RATFOR for portability between systems. To date, the language has been designed and implemented through the syntax checking stage.

E-5. M68K/Versabus Winchester Disk and Controller

Personnel: M. W. Browder, BCL
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S. M. Moore, BCL

Support: RR 00396
RR 01380
HS 03792

Testing and evaluation of two interfaces between the M68000 Versamodule system and Shugart model SA1404 controller have continued. Software was written to interface the controller through the parallel input/output port of the Versamodule and to test the controller and Shugart model SA4008 14-inch 28 Mbyte disk. As expected, the data transfer rate between the Versamodule system and Shugart controller was low because of the software overhead. Initial testing revealed no problems with the disk or controller other than a soft error in one sector of the disk.

In an effort to achieve a higher data transfer rate, a Charles River Data Systems CC-1 selector channel interface was purchased. This board provides a DMA interface between the Versamodule system and the Shugart controller. Modifications were made to the Versamodule monoboard computer, off-board RAM and selector channel interface to make the CC-1 board compatible with our Versamodule system and Shugart controller. More complete testing and evaluation of the Charles River selector channel board are in progress.

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

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Support: RR 00396
RR 01380

A Motorola MC6802 microprocessor-based interface to the Biomation 8100 waveform recorder has been implemented to provide a convenient means for communicating between a general host computer and the recorder. The Biomation 8100 recorder samples waveforms at rates up to 10^7 samples per second and stores these 8-bit samples in a 2048 x 8-bit memory for display and/or transfer to a host computer. The interface accepts mnemonic commands over the IEEE-488 Instrument Bus, interprets these commands and then sends the translated commands to the waveform recorder. After the recorder has sampled a waveform, the interface supervises the transfer of the sampled data between the Biomation 8100 and the host computer.

E-7. Optical Communication Experiment

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Support: RR 00396
RR 01380
Washington University

An experiment has been designed, constructed, and performed which measures several of the turbulence related propagation characteristics of an open-beam, atmospheric, laser-communication link between the engineering school and medical school of Washington University.

The experiment utilized a 5.25 mW HeNe CW laser with an output beam expanded to 5.3 cm in diameter at the engineering school. The focused beam spot was positioned via a remote controller onto a 5.3 cm diameter Fresnel lens located 4.19 Km away at the Computer Systems Laboratory within the medical school complex. The propagation path averaged 30 m above a public park. A minimum spot diameter of only 0.6 m was possible due to the quality of the positioning mirror. The optical signal was filtered by a 10-Angstrom interference filter and detected by a high-efficiency solar cell. The resulting photocurrent was amplified, low-pass filtered to 2.2 Khz, and sampled by a 12-bit analog-to-digital converter controlled by a LSI 11/2 microcomputer. Analysis of the channel characteristics due to clear-air turbulence, solar background, and atmospheric absorption was performed by the microcomputer.

Maximizing the signal-to-noise ratio at the detector was not a goal of the experiment although typical values of 35 dB and 80 dB were measured during very clear weather during day and night measurements, respectively. The log-amplitude variance of the optical signal is a necessary channel statistic for an accurate communication-channel performance estimate. Daytime values of this statistic saturated at 0.2 due to focused-beam propagation effects, and much lower measured log-amplitude variance was measured at night. Coherence time measurements indicate a 4- to 6-millisecond fading correlation-time. The power spectrum of the irradiance fluctuations indicates a -8/3 power law with frequency, with slight variations due to weather conditions, as predicted by various theoretical works.

The measurement results at 632.8 nm have been extrapolated to the near-infrared, and an experimental communication link is being designed to operate at an information rate of 1 Mbps utilizing pulse-position modulation and convolutional coding of the data. The design is to be optimized for minimum probability of an information-bit error. The goal of this study is to design and implement an efficient, high data-rate gateway between local-area networks on each campus. An operating link would provide useful experimental means of evaluating various coding and modulation techniques. The experiment described herein is the first step towards reaching this goal, and it is hoped that further research will result in a useful optical-communication link.

E-8. An Experimental Local-Area Network: TERRANET

Personnel: A. J. Gray, BCL
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Support: RR 00396
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Considerable progress has been made during the past year in the development and implementation of a modest local-area network, TERRANET,[1] to support computing via remote terminals and medium-speed inter-computer communication. The usefulness of such local networks has been confirmed by the proliferation of commercial offerings being introduced. Cost and actual availability of commercial local-area networks (LANs) have mitigated against their application at this laboratory, and provided the rationale for this experiment. Insights developed during the implementation phase should lead to the definition of design and evaluation aids for LAN protocols.

As presently designed, TERRANET provides up to 15 virtual circuit data channels between a maximum of 30 stations at a speed of 9600 bps using time-division-multiplexing. Alternatively, TERRANET may be configured to support more stations if lower data rates per channel are permissible. The network consists of two principal functional elements: a microprocessor-based "tap unit" which implements data-link level functions and end-to-end connection supervision, and a cable-insert unit which provides access to the coaxial cable trunk through which TERRANET transports data and synchronization signals. Tap units are connected through a system of optically isolated RS-422 lines to their corresponding cable inserts. Network synchronization is maintained by a commercially available television sync-generator located at one end of the TERRANET coaxial cable, coupled to the cable by a special driver circuit. Although synchronization is centralized, control of the TERRANET system is a fully distributed peer protocol.

During the summer of 1981 four prototype tap units were constructed using Augat wirewrap techniques, a first-generation cable-insert PC board fabricated, and an initial implementation of the network software written and tested. The coaxial trunk cable was installed through all three levels of BCL and through the basement, approximately halfway to the Computer Systems Laboratory (CSL). This pilot system operated successfully during most of fall 1981.

In December 1981 a major revision of the TERRANET data-link-control protocol was made which increased the data rate through each virtual circuit on the network from the original 4800 bps to 9600 bps. Construction was also initiated on four additional wirewrapped tap units[2] which incorporated several design enhancements over the original tap units, bringing the number

of tap units on the system to eight. The eight-unit configuration was tested for data-transport reliability with encouraging results. The TERRANET cable was also extended to the third floor of CSL.

A printed circuit board was then designed for the tap units by a commercial firm,[3] and a new four-port cable-insert board was developed. Software for the tap units was rewritten to make them more user-oriented[4] and to streamline several aspects of the data-link-control protocol. Through June 1982, twenty-two tap units and ten four-port cable inserts were constructed, most of which were added to the system. A gateway tap unit for the interconnection of two TERRANET systems also was constructed and tested.

TERRANET has been successfully utilized to "download" M68000 systems from UNIX-based hosts and transfer files between RT-11 microcomputers and RSX-11 hosts. Future plans include revisions to cable-insert hardware and tap-unit software which will enhance the reliability of TERRANET virtual circuits under conditions of power-line transients and radiated interference. Efforts to improve documentation of the TERRANET protocols and software continue. Binary-file transfer capability will soon be added to complement ASCII-file transfer capability provided by the TERM transport program.[5]

At the present time TERRANET provides a flexible interconnection among eight video terminals, eight processors, and a dial-up modem, significantly enhancing access to local computing resources.

1. A. J. Gray and G. J. Blaine, "TERRANET: A Modest Terminal-Processor Interconnect for the Laboratory Environment," 7th Conference on Local Computer Networks, Minneapolis, MN, October 11-13, 1982.

2. A. J. Gray, "TERRANET: Wirelist Units Construction Details," BCL Working Note 20, February 1982.

3. A. J. Gray, "TERRANET - Printed Circuit Board Component Designations and Assembly Procedures," BCL Working Note 26, May 1982.

4. A. J. Gray, "A User's Guide to TERRANET," BCL Working Note 25, April 1982.

5. D. W. Stein, Jr., "TERM Terminal Control Program," BCL Working Note 30, May 1982.

E-9. Digital Radiology Studies

Personnel: J. R. Cox, Jr., BCL, Computer Science and Computer Systems Laboratory
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The transformation of radiographic image sequences to the digital domain provides opportunities for enhancing both interpretation and management of diagnostic information. Integration of the various imaging and diagnostic modalities to provide an environment capable of delivering the promised medical benefits holds considerable challenge for both the medical and technological communities.

The basic activities and equipment related to the acquisition, transport, display and archiving of the radiological information can be viewed as a picture archive and communication system (PACS). The canonic form of a PACS includes three classes of nodes interconnected by a high-bandwidth digital network. The first class of nodes includes all image sources: computed tomography (CT), nuclear medicine, ultrasound, digital subtraction angiography and eventually chest and other radiographs. The picture archive may be centralized or distributed, but it seems likely that this second class of nodes will be heavily dependent on the new technology of optical disks to provide the dense packing of information required. Picture-viewing stations that incorporate image processing responsive to the radiologist's needs represent the third class of nodes on the network. The functional characteristics of these stations are just emerging, but rapid response seems to be a high-priority requirement whether the image to be viewed is in a distant archive or has already been retrieved but needs to be processed before viewing.

A preliminary design study[1] has been carried out for a distributed picture archiving and communication system (PACS) for the Mallinckrodt Institute of Radiology. The study develops design equations for three layers of a picture network and examines the estimated flow of digital images between a multiplicity of picture sources, picture archives, and picture viewing stations.

A proposed architecture was suggested to meet the design goals of such a network. It has been designed against the background of a set of design equations for PACS and estimates of current image generation and retrieval activity at MIR.

Some of the conclusions of this analysis include the following:

1. Systems with great bandwidth will be required to handle the retrieval of multi-image studies during peak periods of retrieval activity. Image retrieval must be accomplished quickly and, for a system to be practical,

response times must be comparable to those of any interactive computer system, a maximum of a few seconds.

2. Protocols for error detection and retransmission can be accomplished at little cost given currently achievable bit-error rates.

3. Of the various network architectures considered, a store-and-forward discipline seems ill-suited to PACS design. By comparison, broadcast local networks have some important advantages for picture service.

4. Modular network architectures, capable of reacting to growth and changes in traffic patterns, are essential. Partitioning the network into subnets will reduce bandwidth requirements and increase response time by distributing network traffic.

5. Much work remains to be done including the physical and conceptual design of an archiving system capable of providing adequate response times, the evaluation of suitable data-compression algorithms, the design of inexpensive image-display stations, and the design of efficient network-interface units to buffer data as it is transferred between the network, source, and archive.

The layered approach to the design of computer networks has been applied to a picture archiving and communication system for radiology. The first three layers (physical, picture link, and picture network) have been analyzed. The resulting equations have been applied to typical data obtained from the Mallinckrodt Institute of Radiology. The two-level interconnect described seems well-suited to our needs, but much work remains to be done.

1. J. R. Cox, Jr., G. J. Blaine, R. L. Hill, and R. G. Jost, "Study of a Distributed Picture Archiving and Communication System for Radiology," Proceedings of the First International Conference and Workshop on Picture Archiving and Communications Systems (PACS) for Medical Applications, Proceedings of SPIE, vol. 318, pp. 133-142, January 1982.

E-10. A Broadband Cable Distribution System for Radiology

Personnel: G. J. Blaine, BCL
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R. G. Jost, M.D., Radiology
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Support: RR 01380
Washington University

A design study of a pilot cable system to transport analog and digital radiology pictures and support terminal-to-computer digital data transmission

has been completed. A dual-cable system, separate inbound and outbound cables, with a head-end configured at the 12th floor of the Mallinckrodt Institute of Radiology (MIR) will provide a trunk system which traverses the core of the MIR building and extends through the steam tunnels to a junction point near the power plant. The junction point allows branches to the A&P warehouse (future site of the film library) and the Biomedical Computer Laboratory.

Initial installation will include branches to radiology resources located within the West Pavilion of Barnes Hospital, and the 3rd and 4th floors of MIR and to the Biomedical Computer Laboratory.

The dual-cable 400 MHz system utilizes "off-the-shelf" cable television components to provide approximately 50 channels, based on frequency multiplexing and an allocated bandwidth of 6 MHz each channel. The system will provide an environment for the evaluation of commercial digital transmission equipment in addition to supporting experiments related to digital picture networking and archiving studies (E-9). A design tool, written in BASIC, was developed to assist in attenuation calculations and management of the tree-structural network topology. Installation and evaluation is planned for the fall of 1982.

E-11. Data Compression Studies: ECG and Digitized Autoradiography

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K.-H. Tzou, BCL and Electrical Engineering

Support: RR 00396
Washington University

Data compression or source coding is useful in situations where the amount of storage required for a given biomedical data set or rate required to transmit biomedical information sources over a standard communication channel such as a telephone must be reduced. The source coding issue can be divided into the noiseless source coding problem, in which perfect reproduction of the original source is required, and source coding with a fidelity criterion, in which a sufficiently accurate reproduction of the source is required as measured by a fidelity criterion that compares the original and reproduced sources. A preliminary study of these two problems was performed on two different information sources of biomedical interest: 1) noiseless source coding of digitized ECG signals, and 2) source coding with a fidelity criterion of digitized silver-grain images from autoradiography studies.

For the noiseless source coding problem, a general experimental methodology was developed[1] to find suboptimal but good variable-length to variable-length codes. Several specific algorithms were studied and experimental tests determined that an algorithm which attempts to dynamically extend the most probable node was, overall, the best performing algorithm. Application of these algorithms to ECG test-data sets suggested that current

techniques which use first and second differences are yielding nearly optimal performance. A more in depth study was considered[2] and showed that a further gain of about 20 to 30% could be achieved in principle but is too computationally complex to be realized. Thus we conclude that there is little improvement to be achieved for ECG data compression techniques which examine only local sample points.

For the problem of source coding with a fidelity criterion, a methodology was developed for finding trellis-encoding data-compression techniques for digitized silver-grain images.[3] A 1 bit/pixel rate was achieved with negligible degradation in picture quality as determined by human observers and with negligible differences in the counts obtained by silver-grain counting algorithms. A two-dimensional transform coding technique was examined and compared to the trellis-encoding technique. For silver-grain images, the trellis-encoding algorithm is superior in reproducing the silver-grains while the two-dimensional transform coding technique is superior in reproducing the background material. In conclusion, a 1 bit/pixel rate is achievable for silver-grain images, yielding an overall compression of about 1 to 8. This study also indicated the need to develop better visual fidelity criterion models for human observers.

1. N. R. Kolb, "An Experimental Approach to Compressibility Estimation and Variable-length to Variable-length Coding," Biomedical Computer Laboratory Monograph No. 412, December 1981.

2. J. G. Dunham, "Coding Large Alphabet Sources with ECG Applications," Proceedings of the 34th Annual Conference on Engineering in Medicine and Biology, Houston, Texas, p. 69, September 21-23, 1981.

3. K.-H. Tzou and J. G. Dunham, "A Preliminary Study of Iterative Code Design for Silver-Grain Images," Biomedical Computer Laboratory Monograph No. 407, December 1981.

E-12. Study of the Cutoff-Rate Region for Asynchronous Multiple Access Channels

Personnel: D. L. Snyder, BCL
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Support: RR 00396
ENG 76-11565

The cutoff-rate parameter for a single-user channel was extended to a "cutoff-rate region" for a multiple-user channel. This region is a collection of rates for which reliable communication for all users sharing the channel can be assured, and it is useful for predicting the complexity of the encoding and decoding needed to achieve a specified joint reliability. We find this

cutoff-rate region to be useful in the design of multiple-user communication systems. As an example, for any rate pair in the cutoff-rate region of a two-sender, one-receiver system, we can predict the additional encoding/decoding complexity required without frame synchronization to assure the same reliability as with synchronization. The definition and use of the cutoff-rate region have been reported.[1]

1. P. Narayan and D. L. Snyder, "The Two User Cutoff Rate for an Asynchronous and a Synchronous Channel are the Same," IEEE Transactions on Information Theory, vol. IT-27, no. 4, pp. 414-419, July 1981.

E-13. Compliance with Topical Ophthalmic Therapy

Personnel: D. W. Meltzer, M.D., Ophthalmology
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RR 01380
EY 03579

As described in a previous report (PR 17, F-10) bottles of eyedrops equipped with an electronic recording device are being utilized to investigate the role of non-compliance with suggested therapy in treatment failure of ophthalmic disease. At the present time more than 100 patients have been included in the study and the monitor bottles have been dispensed over 200 times. At least three additional years of data acquisition are planned.

Software to read and analyze the 4096 bits of data collected by the monitor bottle has been successfully implemented and is being routinely used. The software runs on a PDP 11/34 under RSX-11M and provides the following functions to a user in the form of indirect commands:

1. @BOT allows a user to read in 4096 bits of data from a memory chip incorporated in the dropper bottle. It also prompts the user for all associated patient information. The entire collection of data is then stored on disk for future review and analysis.

2. @DIR allows the user to obtain a directory of all patients currently contained in the database. Each entry includes the patient name and identification number. This listing is automatically routed to the lineprinter.

3. @TDIR is the same as @DIR except that the directory is routed to the user's terminal.

4. @PBOT allows the user to retrieve a hardcopy listing of any patient data file previously created.

5. @UPDATE allows the user to modify the contents of patient header information associated with any patient data file.

6. @CRTRV allows the user to generate an IBM-compatible tape consisting of selected patient files.

7. @DUMP dumps the directory of a tape generated by @CRTRV to the line printer.

8. @CLEAN rids the disk of any unnecessary temporary files which may have been generated by previous runs.

A complete documentation package for this software system is forthcoming.

E-14. An Automated System for the Monitoring of Patients with Epidural Electrode Arrays

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The purpose of this project is to develop a system which will permit simultaneous recording of the EEG and sensory evoked responses from patients in whom epidural electrode arrays have been implanted for the purpose of localizing an epileptogenic focus.

The system consists of three parts, as shown in the block diagram (Figure 1). An automated switching matrix allows us to select EEG data or evoked responses from up to 52 electrodes and to switch rapidly from one set of input signals to another. The subsystem for computer-assisted extraction of somatosensory evoked responses (CAESER) will be used to acquire, store, and display the evoked-response data. The patient monitoring subsystem, based on a remotely located minicomputer, will be capable of monitoring the patient's EEG activity, detecting a seizure, and generating a videotape showing the patient and the EEG data side by side. In addition, it will be capable of generating a conventional paper EEG recording. It will have the capacity to store, index, and display on command the EEG activity and patient behavior for a period of several minutes before, during and after each seizure.

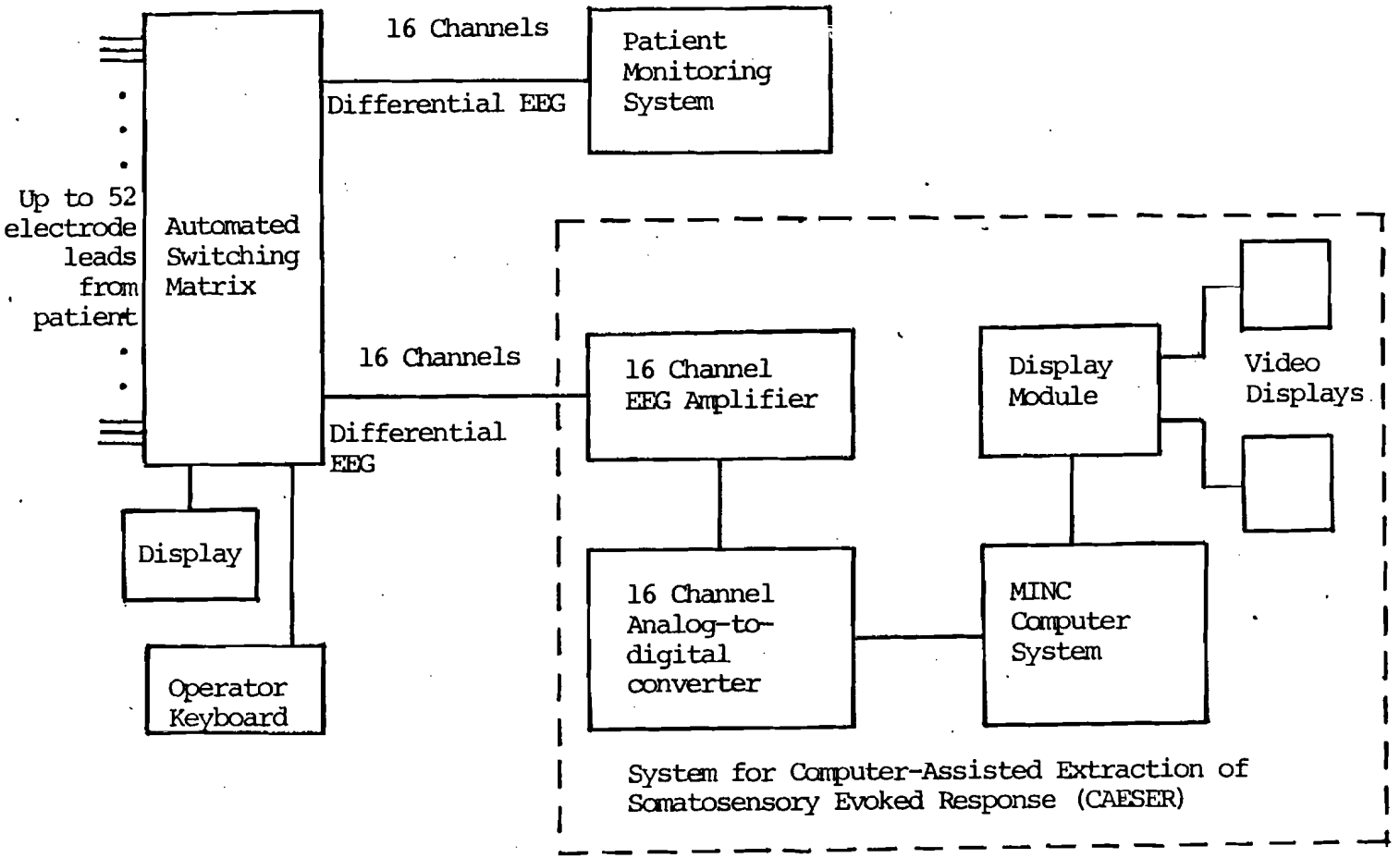

Figure 1. Block diagram of automated system for the monitoring of patients with epidural electrode arrays.

As reported last year (PR 17, F-12), the automated switching matrix has been completed and is now in routine use. It has performed adequately, and only a few minor problems have been encountered.

The CAESER system is currently under development. It consists of a sixteen-channel EEG amplifier, a sixteen-channel analog-to-digital converter, a Digital Equipment Corporation MINC microcomputer system to perform signal averaging, data manipulation, and storage, and a video display module which is used to plot the evoked responses on standard television monitors.

A prototype EEG amplifier reported earlier (PR 16, F-2; PR 17, F-12) was found to have insufficient common-mode rejection at 60 Hz in the clinical environment. We plan to use sixteen Grass Instrument Company 8A5 EEG amplifiers, which are currently in use in our EEG machine, until an acceptable amplifier can be designed, built, and tested.

Construction and initial testing of the analog-to-digital converter and its associated MINC interface have been completed. The MINC computer will be used to conduct final testing on this device.

The video display module has been built and hardware testing was completed in June 1982. The system is controlled by an M6800 microprocessor, software for which is currently under development.

Software for system control and data storage is being developed on the MINC, running under the RT-11 operating system. The majority of the software is being written in RATFOR, a structured dialect of FORTRAN. System control during acquisition of the somatosensory evoked response (SER), when speed is critical, will be provided by an assembly language program.

An initial system should be on line in August 1982. Further plans for this aspect of the project include addition of a 16-channel EEG amplifier which will be controlled by the user through the MINC, and a second generation of MINC software which will allow the system to be easily operated by medically-oriented users.

The patient monitoring system will be based on a Digital Equipment Corporation PDP-11/34 minicomputer located in McMillan Hospital which will be linked to equipment near the patient via a digital communication system. The PDP-11/34 was installed in December 1981 and has been used since then in the development of M6800 software with the FOCRAS set of development programs (PR 17, F-1). Full scale design and development of this system should be well underway by early 1983.

E-15. Implementation of a Control Unit for Use in Retinal Experiments

Personnel: R. W. Hagen, BCL
A. I. Cohen, Ph.D., Ophthalmology

Support: RR 00396
RR 01380
EY 00258

This control unit was implemented in support of research work which seeks to determine the kinetics of light-induced changes in photoreceptor segments of intact retinas. Experiments which support this research are designed to investigate transient biochemical changes in the receptors during photo transduction. These biochemical processes are quenched by freezing with liquid helium. An apparatus was purchased and modified to produce rapid freezing of the retina sections. A control unit was implemented and interfaced to the purchased apparatus. This unit enables the investigator to precisely adjust the light exposure time. After selecting the exposure time the investigator begins each experiment by pushing a button on the Control Unit which sequences the light source timing and the retina freeze timing.

E-16. Video Camera Evaluation

Personnel: R. W. Hagen, BCL
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C. W. Boylan, B.S., Mechanical Engineering
R. A. Gardner, Ph.D., Mechanical Engineering

Support: RR 00396
RR 01380
HL 12839

Three types of video cameras were evaluated for application in a research project which seeks to characterize an erythrocyte's capacity to change shape in response to rapidly varying flow conditions. Normal and diseased cells were placed in an apparatus which allows the cells to remain stationary in space while experiencing various flow-shear conditions. Magnified images of these erythrocytes were recorded on video tape for analysis. Since the research objective is to study cell deformation during rapidly varying flows, the time discrimination and the resolution of the image recording system are important considerations.

The resolution and time discrimination achievable with standard video tape recorders satisfies the research needs. However, the video camera has limited the overall performance of the recording system. Experiments were performed with the image of interest illuminated by a strobe light which was

synchronized to the video frame rate of the recording system. A nuvicon type camera had inadequate response time since it took five frame times for the image of an illuminated cell to disappear. A charge injection camera (PR 16, G-9) with superior response time provided unacceptable resolution. The plumbicon type tube was finally selected because its resolution and response time produced recorded images which satisfied the time discrimination and resolution needs.

VI. INDUSTRIAL COLLABORATION

Industrial collaboration provides a mechanism for the deployment of laboratory developments and benefits the staff by keeping abreast of the practical considerations of reliability, maintainability and cost.

A collaborative drug study, "A Multiprotocol Study of Encainide Hydrochloride (Encainide)" sponsored by Mead Johnson is underway at the Jewish Hospital of St. Louis and 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 normal cardiac index. In clinical studies, Encainide suppressed ventricular arrhythmias following either single or divided doses ranging from 25-150 mg. Study protocols are detailed in a previous report (PR-17, VI). Long-term electrocardiographic recordings are obtained in order to assess the efficacy of Encainide on arrhythmias. The recordings obtained at Jewish Hospital are analyzed by the Biomedical Computer Laboratory's Argus/2H arrhythmia analysis system. Study-relevant data are extracted from Argus/2H printed summaries by personnel at Jewish and forwarded to Mead Johnson. To date, the Argus/2H system has analyzed 189 recordings from 21 patients.

The Biomedical Computer Laboratory had planned to use the Argus/2H arrhythmia analysis system to process long-term ECG recordings for the American Critical Care-sponsored study of a "Comparison of the Efficacies of Bretylol and Procainamide in the Treatment of Ventricular Arrhythmias Resistant to Lidocaine." Described in detail last year (PR 17, VI), the study was subsequently terminated by American Critical Care because of the unavailability of a sufficient number of patients.

During the past year we have continued to digitize long-term ECG recordings for IBM Biomedical Systems on a fee-for-service basis. A total of 93 recordings have been digitized as of June 30, 1982.

VII. TRAINING ACTIVITIES

Training activities of the Biomedical Computer Laboratory are directed toward the goals of informing the local and national scientific communities about resource projects and facilities and of instructing a broad spectrum of people in the application of advanced computer-techniques to problems in clinical medicine and biological research. Training activities include the teaching of formal courses at the School of Medicine and the School of Engineering as well as supervision of graduate students by Laboratory staff, seminars relating to resource projects and applications, individual and small-group training about resource facilities, and national workshops and symposia on topics of interest and importance to the resource and community.

The bringing together of biomedical scientists, engineers, and computer scientists provides important cross-fertilization between disciplines. In these settings, students and staff find the need and opportunity to test the relevance of theory and the usefulness of technology in applications to real problems. Also, the biomedical scientists are aided in learning new techniques for acquiring useful information. To this end, some of the courses offered are addressed to biologists without strong technical backgrounds who want and need a below-the-surface appreciation of biomedical computing. Laboratory personnel also participate in regularly scheduled conferences in the clinical departments where both the biological and technological issues are examined.

The establishment of a fee-for-service facility, the Medical Computing Services Group, provides comprehensive support to biomedical investigators for research database activities. The focus of that facility has fostered a natural transition to their sponsorship of the non-credit MUMPS course previously conducted by our Laboratory. Other non-credit courses continue to be offered by the Laboratory. These include "Introduction to Programming the Laboratory Computer" and "Computers in Medicine."

VIII. SEMINARS

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

"DEC Microcomputer Products" July 9, 1981	Mr. Mike Taterka Mr. Bill Sherman Digital Equipment Corporation St. Louis, Missouri
"Sights at SIGGRAPH '81" August 11, 1981	Mr. Alex Gray Biomedical Computer Laboratory Washington University St. Louis, Missouri
"Adaptive Pulse-Echo Imaging for Quantitative Ultrasonic Tissue Characterization" August 11, 1981	Mr. K. V. Gurumurthy Department of Electrical Engineering Washington University St. Louis, Missouri
"Local Networking Research at The Johns Hopkins University Applied Physics Laboratory October 27, 1981	Mr. Steve Kahn Applied Physics Laboratory The Johns Hopkins University Baltimore, Maryland
"Quantitative Measurements with Positron Computed Tomography" November 2, 1981	Dr. Henry Huang Division of Nuclear Medicine University of California Los Angeles, California
"Computer Processing of Nuclear Medicine Cardiac Studies" November 20, 1981	Dr. Thomas R. Miller Department of Radiology Washington University St. Louis, Missouri
"System Design Considerations for Acquisition of Canine Cardiac Electrograms" December 7, 1981	Mr. Bert H. Tanaka Biomedical Computer Laboratory Washington University St. Louis, Missouri

"An Automated Instrument System for Quantitative Evaluation of Neuro-anatomical Autoradiographs"

December 9, 1981

Mr. Alex Gray
Biomedical Computer Laboratory
Washington University
St. Louis, Missouri

"Medical Imaging Activities at the Royal Marsden Hospital"

April 20, 1982

Dr. Roy E. Bentley
Royal Marsden Hospital
Sutton, Surrey
England

"An MMU for the Motorola 68000"

June 2, 1982

Mr. David Bridger
The Computer Systems Center of Hazelwood
Hazelwood, Missouri

"Introduction to Picture Archiving and Communication Systems for Radiology"

June 25, 1982

Dr. G. J. Blaine
Biomedical Computer Laboratory
Washington University
St. Louis, Missouri

IX. PUBLICATIONS AND ORAL PRESENTATIONS

Arthur, R. M., "An Adaptive Beamformer for Ultrasonic Tissue Characterization," presented at the Seventh International Symposium on Ultrasonic Imaging and Tissue Characterization, National Bureau of Standards, Gaithersburg, Maryland, June 6-9, 1982.

Bergmann, S. R., "Biomedical Application of Positron Emission Tomography," presented at the NHLBI Workshop on Cardiovascular Instrumentation: Applicability of New Technology to Biobehavioral Research, Houston, Texas, May 16-19, 1982.

Bergmann, S. R., Hack, S. N., and Sobel, B. E., "Redistribution of Myocardial ^{201}Thallium without Reperfusion: Implications Regarding Absolute Quantification of Perfusion," American Journal of Cardiology, vol. 49, pp. 1691-1698, 1982.

Bergmann, S. R., Lerch, R. A., Fox, K. A. A., Ludbrook, P. A., Welch, M. J., Ter-Pogossian, M. M., and Sobel, B. E., "The Temporal Dependence of Beneficial Effects of Coronary Thrombolysis Characterized by Positron Tomography," American Journal of Medicine, in press.

Bergmann, S. R., Lerch, R. A., Mathias, C. J., Sobel, B. E., and Welch, M. J., "Visualization of Coronary Thrombus in vivo with ^{111}In-Platelets," Circulation, vol. 64, supplement IV, p. IV-33, 1981 (abstract).

Bergmann, S. R., Lerch, R. A., Welch, M. J., Ter-Pogossian, M. M., and Sobel, B. E., "The Temporal Dependence of Restoration of Myocardial Metabolism by Thrombolysis Assessed with Positron Emission Tomography," Circulation, vol. 64, p. IV-195, 1981 (abstract).

Bergmann, S. R., Mathias, C. J., Sobel, B. E., and Welch, M. J., "Evaluation of Thrombolytic Therapy in Coronary Artery Thrombosis: Scintigraphic Detection with the Use of In-111-Labeled Platelets," Proceedings of the Third World Congress on Nuclear Medicine and Radiation Biology, in press.

Blaine, G. J., "Digital Image Archiving and Communication Systems," invited tutorial presented at the International Symposium and Tutorial on Digital Video Image Techniques in Cardiovascular Radiology, Kiel, Germany, May 24-25, 1982.

Blaine, G. J., Ficke, D. C., Hitchens, R. E., and Holmes, T. J., "Data Acquisition Aspects of Super-PETT," IEEE Transactions on Nuclear Science, vol. NS-29, no. 1, pp. 544-547, February 1982.

Christlieb, I. Y., Clark, R. E., and Sobel, B. E., "Three Hour Preservation of the Hypothermic Globally Ischemic Heart with Nifedipine," Surgery, vol. 90, pp. 947-955, 1981.

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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.

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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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405	Gurumurthy, K. V.	Adaptive Pulse-Echo Imaging for Quantitative Ultrasonic Tissue Characterization	8/81
406	Snyder, D. L.	What Performance Gain Does an Emission Tomography System Having Time-of-Flight Measurements Offer?	11/81
407	Tzou, K. Dunham, J. G.	A Preliminary Study of Iterative Code Design for Silver-Grain Images	12/81
408	Tanaka, B. H.	System Design Considerations for Acquisition of Canine Cardiac Electrograms	12/81
409	Hermes, R. E. Cox, Jr., J. R.	Modeling Detector Performance: An Approach to Arrhythmia Detection System Evaluation	9/81
410	Clark, K. W. Hermes, R. E. McLear, P. W. Mead, C. N. Thomas, Jr., L. J.	The ARGUS/2H Approach to Supra-ventricular Arrhythmia Analysis	9/81

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412	Kolb, N. R.	An Experimental Approach to Compressibility Estimation and Variable-Length to Variable-Length Coding	12/81
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13	Esrig, J. A.	DNASCN - Gel Data Manipulation System	7/81
14	Beecher, D. E.	Documentation Package - Interactive Region of Interest Software - PHASE I	10/81
15	Holmes, T. J.	A Simplified Approach to Confidence Weighted Pre-Image Construction for Time-of-Flight Positron Emission Tomography	11/81
16	Tanaka, B. H.	A Document on ASSEMBLER TED, a Rockwell 6502 Text Editor and Assembler	1/82
17	Tanaka, B. H.	A Document on DASS3, the BASIC Program in the PET of the Data Acquisition System at Jewish Hospital	1/82
18	Tanaka, B. H.	A Document on DASSMTEXT, the Assembler Program in the PET of the Data Acquisition System at Jewish Hospital	1/82

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20	Gray, A. J.	TERRANET - Local Computer Net	2/82
21	Blaine, G. J. Browder, M. W.	An Overview of the Data Acquisition and Analysis for the Dementia VEP Studies Evoked Potentials	2/82
22	Clark, K. W.	List of References Chronicling ECG Rhythm Analysis Activities at BCL	3/82
23	Beecher, D. E.	Documentation Package, Screen Oriented Library Routines, Version I	4/82
24	Beecher, D. E.	SUPER PETT I: Software Support	4/82
25	Gray, A. J.	A User's Guide to Terranet	4/82
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27	Beecher, D. E.	Pixel-Based Region Construction and Filling Algorithms	5/82