1969

Progress Report No. 5

Biomedical Computer Laboratory

PROGRESS REPORT

No. 5

1 JULY 1968 - 30 JUNE 1969

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

BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

PROGRESS REPORT NO. 5

1 July 1968 - 30 June 1969

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I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes work done during the period from July 1, 1968 through June 30, 1969. The Biomedical Computer Laboratory collaborates with research investigators throughout the Washington University School of Medicine in the application of advanced computer techniques to research problems in biology and medicine.

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

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

A final class of applications requires extensive use of large-scale computational services. Many investigators are assisted in their research through the use of generalized numerical, non-numerical, and statistical routines. This work is carried out in part by staff members of BCL in addition to those members of the Medical School, Division of Bio-Statistics, under the direction of Dr. Reimut Wette, and the University Computing Facilities Scientific Data Processing group.

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

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

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

The National Advisory Panel to advise WUCL on health-related activities is presently composed of the following membership:

H. K. Beecher	Dorr Professor of Research in Anaesthesia	Harvard Medical School
W. H. Danforth	Vice-Chancellor for Medical Affairs	Washington University School of Medicine

K. F. Killam	Professor of Pharmacology	Stanford University
F. M. Richards	Professor in Molecular Biophysics and Chemistry	Yale University
R. S. Snider	Professor of Anatomy and Director of Center for Brain Research	University of Rochester

The Panel held its second meeting on April 7, 1969. The agenda included a review of a proposed summer workshop on molecular graphics, an initial step in a national program of collaborative research. The Advisory Panel will meet periodically with the WUCL Coordinating Committee to review developing techniques and to advise upon desirable areas of application.

II. SOURCES OF SUPPORT

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

FR 00396	A Resource for Biomedical Computing

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

AM 04082	Regulation of Glucose Metabolism
AM 10025	Water and the Electrolyte Transport in the Toad Bladder
AM 13332	Metabolic Regulation and Interacting Enzyme Systems
CA 10435	Clinical Cancer Radiation Therapy Center
CA 10926	Use of Heavy Isotopes In Biological Research
FR 05389	Quantitative Computer Analysis of Bone Radiographs
HE 00082	Clinical Experimental Research In Respiration
HE 05435	Cardiovascular Research and Training Center
HE 09528	LINC Computer Study of Fetal Electrocardiograms
HE 10406	Enzymatic Mechanism In Lipid Metabolism
HE 11034	Circular Regulation and Myocardial Contraction
NB 03856	Auditory Communication and Its Disorder
NB 06833	Interdisciplinary Stroke Program
NB 12237	Regional Cerebral Function; Radioisotopic Methods

An Atomic Energy Commission grant and a National Science Foundation grant helped to support portions of several projects:

AT 01653	Parathyroid Scanning
NSF 57265	Crystollographic Studies of Protein Structure and Function of Calf Liver Cytochrome B_5

III. PERSONNEL

EMPLOYEES

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

Director

Jerome R. Cox, Jr. Sc.D.

Assistant Director for Engineering

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

Administrative Officer

Edward L. MacCordy, M.B.A.

Research Associates

Richard A. Dammkoehler, M.S.
William F. Holmes, Ph.D.
Maxine L. Rockoff, Ph.D., since September 1, 1968

Research Assistants

James M. Baker, B.S., since January 27, 1969
Gerald R. Barthel, B.S., since March 1, 1969
G. James Blaine, M.S.
Andrew L. Bodicky, B.S.
David A. Bridger, B.S., since October 1, 1968*
A. Maynard Engebretson, Sc.D.
Donald H. Glaeser, Sc.D.
Rexford L. Hill, III, M.S.
Monte D. Lien, M.S.
Michael D. McDonald, B.S.
Donald J. Manson, Ph.D.*
Joanne Markham, B.A.
Floyd M. Nolle, M.S.
James M. Pexa, B.S., since July 15, 1968
Elizabeth Van Patten, B.S.
Richard A. Zacher, Ph.D., since February 15, 1969

Programmer

Madhukar Bhide, A.B.

Technical Assistant

J. Claude Bramwell, B.A.

Engineering Assistant

Glen M. Roa

Programming Assistants

Leonard Berger, since September, 1968*
Adonis R. Black, B.S., since June 1, 1969
Lawrence K. Bolef
Douglas W. Clark
James E. Crawford, B.S.
Mark Drazen
William V. Glenn, Jr., B.S.*
David Kaplan, since June 23, 1969
Richard A. Kolde, since June 9, 1969
Davis M. Swan, B.S., M.D.*
Louis J. West
Steven Ziskind, since June 9, 1969

Project Technicians

H. Dieter Ambos
Stephen M. Rhode

Electronics Technicians

Charles R. Buerke
Christopher R. Fraction, since April 28, 1969
Kenneth L. Kunkelmann
Nizar A. Mullani, B.S., since February 5, 1969

Machinist

George C. W. Meyer*

Librarian

Allie Allmon, B.S.

Office Clerk

Allen Sanders*

Visiting Scientist

Roy E. Bentley, Ph.D., July 1-August 30, 1968

Secretaries

Merry M. Ambos
Virginia M. Bixon
Christine Guerrero, since October 1, 1968
Wanda J. Meek
Sheryl L. Sharp

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

Changes in Personnel

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

Madhukar Bhide, terminated April 18, 1969
David A. Bridger, terminated January, 1969
J. Claude Bramwell, terminated September 30, 1968
A. Maynard Engebretson, terminated May 31, 1969
Donald H. Glaeser, terminated June 14, 1969
Stephen M. Rhode, terminated May 31, 1969
Sheryl L. Sharp, terminated August 23, 1968
Richard A. Zacher, terminated April 30, 1969

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

Lawrence K. Bolef, returned to school August 30, 1968
Douglas W. Clark, returned to school July 31, 1968, rehired June 27, 1969
James E. Crawford, returned to school August 30, 1968
Gerald C. Rossi, returned to school August 30, 1968
Louis J. West, returned to school August 30, 1968, rehired June 16, 1969

RESEARCH COLLABORATORS

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

Washington University

R. Aaronson, Biochemistry
L. J. Banaszak, Ph.D., Physiology and Biophysics
J. M. Barnes, B.A., Pediatrics
M. R. Behrer, M.D., Pediatrics
S. J. Birge, M.D., Metabolism
V. Bleisch, M.D., Pathology

D. A. Bridger, Information Processing Center
L. Brock, Ophthalmology
J. Burgess, Electronic Shop
G. R. Drysdale, Ph.D., Biochemistry
R. P. Eaton, M.D., Metabolism
J. E. Eichling, M.S., Radiology
J. Elovson, Ph.D., Biochemistry
J. M. Enoch, Ph.D., Ophthalmology
A. Feldman, Ph.D., Radiology
N. K. Flammang, M.S., Radiology
H. Fotenos, Radiology
C. Frieden, Ph.D., Biochemistry
T. L. Gallagher, Sc.D., Information Processing Center
S. Goldring, M.D., Neurosurgery
J. Jeffers, R.N., Barnes Hospital
T. Kendrick, Graduate Student, Biochemistry
M. Levine, Ph.D., Physiology and Biophysics
S. P. Londe, M.D., Surgery
V. Luthra, Mechanical Engineering
E. Massie, M.D., Barnes Hospital
F. S. Mathews, Ph.D., Physiology and Biophysics
J. Mok, Administrative Data Systems
H. T. Narahara, M.D., Biochemistry
G. C. Oliver, Jr., M.D., Medicine
E. J. Potchen, M.D., Nuclear Medicine
G. L. Powell, Ph.D., Biochemistry
W. E. Powers, M.D., Radiology
S. D. Rockoff, M.D., Radiology
A. Roos, M.D., Anesthesiology and Physiology
J. H. Scandrett, Ph.D., Radiology
P. E. Stohr, M.D., Neurosurgery
S. Sutera, Ph.D., Mechanical Engineering
M. M. Ter-Pogossian, Ph.D., Radiology
L. J. Thomas, M.D., Anesthesiology
L. J. Tolmach, Ph.D., Radiology
A. Vose, R.N., Barnes Hospital
G. Wolff, M.D., Medicine
R. B. Woolf, M.D., Obstetrics and Gynecology
A. R. Zacher, Ph.D., CSL

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

Robert Shalek, Ph.D.
Marilyn Stovall

Central Institute for the Deaf

L. L. Elliot, Ph.D.
D. H. Eldredge, M.D.
I. J. Hirsh, Ph.D.
C. S. Watson, Ph.D.

Methodist Hospital, Houston, Texas

David Brooks, M.D.
Michael E. DeBakey, M.D.
C. J. Flynn, M.D.
J. E. Merrill, M.D.

National Cancer Institute, Bethesda, Maryland

Fred Faw
Dwight Glenn
Ralph Johnson, M.D.

Ontario Cancer Institute, Toronto, Canada

Dirk Brinkman
J. R. Cunningham, Ph.D.
William Rider, M.D.

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

Roy E. Bentley, Ph.D.
Joseph Milan

Stanford University, Stanford, California

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

Temple University, Philadelphia, Pennsylvania

K. C. Tsien
John Wright, Ph.D.

University of Chicago, Chicago, Illinois

H. A. Fozzard, M.D.

University Hospital, London, England

J. S. Clifton, M.Sc., A. Inst. P.

<u>University of Maryland, Baltimore, Maryland</u>

Eugene Robinson, Ph.D.
Joe Rose

<u>Yale University, New Haven, Connecticut</u>

A. L. Finn, M.D.

IV. PHYSICAL RESOURCES

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

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

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

During the past five years the laboratory space has been increased by 2762 square feet on the ground floor and 2532 square feet on the second floor of 700 South Euclid, and by 3463 square feet on the second floor of the building just south of the original space. Facilities for computational applications, laboratories, staff offices and a WUCL research library are provided in these acquired spaces. Direct communication with the IBM 360/50 at the Washington University Information Processing Center is provided via phone lines, Programmed Consoles and LINC's.

V. RESEARCH PROJECTS

The reports presented in the following sections are arranged according to the major research areas in which the laboratory has been engaged during the past year. Each report lists the personnel who participated in the research and gives their affiliation. The academic degrees of all BCL personnel are omitted in these lists since this information can be found in Section III. Unless otherwise specified, all organizations and departments listed are part of Washington University. Also listed, by grant or contract number, is the support for each research project. The titles of applicable grants or contracts and the funding agency are provided in Section II.

References to other reports presented herein will be made by section number alone. References to any of the four previous BCL progress reports will be abbreviated thus: (see PR 4, A-1).

A. The Programmed Console

The Programmed Console (PC) is a small stored program computer system especially designed for radiation treatment planning and other graphically oriented tasks. Much of the development of the PC has been reported previously (see PR 2, A-1; PR 3, A; PR 4, A), but a few research projects are presented below describing recent improvements in programs and equipment.

A-1. Utility and Arithmetic Routines for the PC

Personnel: M. D. McDonald, BCL

Support: FR 00396

1) An entirely new version of the Questions and Answers (Q+A) subroutine (see PR 3, A-6) was written. This version is independent of the PC monitor and occupies one-third fewer core locations than its predecessor. A significant saving in the time required for sampling the keyboard and displaying the response character struck was also effected so that it is impossible for the user to type too fast.

2) A very fast single precision fixed point division subroutine (DIV) was written, making use of the iterative equation which was used in the Harvard Mark IV computer.[1] DIV occupies 105_8 words of core. The average time for a division (on a Spear PC) is 3 msec.

3) A floating point output subroutine (FLOPO) was generated for use with the single precision floating point subroutine FLOPS (see

PR 3, A-6). FLOPS format numbers are converted to decimal and printed on the Teletype in FORTRAN E format, i.e.,

$$\pm \text{x.xxx E} \pm \text{yy}$$

4) A set of decimal floating point subroutines was written to perform addition, subtraction, multiplication, and division in decimal on numbers expressed to twenty-one decimal digit precision.

5) Three special purpose display subroutines were written, one to display characters in any of 64_{10} sizes and 64_{10} angles from the horizontal, another to display a set of points as a histogram, and another to display data as points connected by straight lines, using a particularly fast algorithm to draw the lines.

(1) Richards, R. K.,"Arithmetic Operation in Digital Computers, D. Van Nostrand Co., Inc., New York, pp. 279-281, 1955.

A-2. IMP and PC Checkout Programs

Personnel: M. D. McDonald

Support: FR 00396

IMP, the assembler for the PC (see PR 4, A-7), after a period of in-house debugging, was distributed to all of the PC users along with a writeup (BCL Monograph 90) describing its usage.

Work has begun on a version of IMP which will work in collaboration with an IBM 360/50 using its disk storage for IMP manuscript and binary.

Three programs to aid the user in checking out his own PC programs were also written; they are INTERP, TRACE and DEBUG (BCL Monograph 91). Each of these programs is available on a single Datamaster card and runs the program to be debugged interpretively.

INTERP causes interruption of the running of the user's program if an instruction is ever about to be executed at a specified location, or if the contents of a specified location are either modified or set to a specified number, or if an instruction about to be executed is of a specified kind. TRACE causes a Teletype listing of the program flow to be printed. DEBUG yields a Teletype printout of the contents of specified locations if an instruction at a specified location is ever about to be executed.

A-3. LINC-PC Systems

Personnel: M. D. McDonald, BCL

Support: FR 00396

The LINC-PC Systems (see PR 3, A-7) have undergone extensive revisions and additions. Some modifications were made to LAP6, including the addition of eleven special meta commands. Through these meta commands the user may assemble a program for the PC, print out the symbol tables after an assembly, transmit the PC binary from the LINC to the PC, file the PC binary on the IBM 360/50 disc (see E-3), print the manuscript and binary on the Motorola printer, or simulate the running of a PC program on the LINC. A report describing fully the operation of this system and its various components was issued (BCL Monograph 41).

A-4. Datamaster Card Copy Program (CPDM)

Personnel: E. Van Patten, BCL

Support: FR 00396

This is a simplified, one-card, version of the Variable Speed Datamaster Program (VSDM) (see PR 4, A-3). The improved Datamasters now installed on all PC's make it unnecessary to read a card at a speed different from that at which it was written. This facility was deleted, as well as the scatter diagram, leaving a card copy program which determines the number of words on a card as it is read. A word-by-word check is made of a card written. CPDM also expedites the copying of large numbers of cards.

A-5. Test Programs for the Programmed Console

Personnel: G. M. Roa, BCL
A. M. Engebretson, BCL
V. W. Gerth, Jr., BCL

Support: FR 00396

A new set of test programs and accompanying user manual was written, replacing an older version (see PR 3, A-2), written by P. J. Kirwin. Though the new set borrows heavily from the old, the new one is more standardized, easier to use, more thorough and flexible than the older set. In addition, several completely new tests have been added including Lower Memory Test, All Patterns Memory Test and Calcomp Test. The accompanying manual (BCL Monograph 121), gives a description of each test, its use, and an annotated listing of its manuscript.

The new test versions were all written with the IMP assembly program and their manuscripts are stored on Datamaster cards whereas the previous test set used the LINC-PC assembler and LINC tape for manuscript storage.

There are a total of 21 test programs, each contained on a single Datamaster card. Printed on each card is information useful to running and analyzing the test contained on it. This includes the various keyboard options available, error halt locations, running time and start and restart locations.

A-6. Engineering Modifications to the Programmed Console

Personnel: V. W. Gerth, Jr., BCL
J. R. Cox, Jr., BCL
G. M. Roa, BCL
H. D. Ambos, BCL
C. R. Buerke, BCL
K. L. Kunkelmann, BCL

Support: FR 00396

Engineering modifications to improve the reliability and usefulness of the Spear Programmed Consoles have been developed and installed. In addition to these modifications of general applicability, other engineering modifications related to specific application areas are described elsewhere.

Spear PC's from the second production run provided additional flexibility in data transmission format over the original machines by allowing selection of a transmission sequence with least or most significant bit first and selection of start bit sensing. A modification for the machines from the first production run was developed to provide this same flexibility.

The original PC implementation used the REPEAT mode during scope erase with the implication that interrupt operations could not be carried on for the duration of the erase interval (500 msec for 611 scopes). Since this did not allow data transmission during scope erase, the DST instruction was modified to initiate scope erase but not go into the REPEAT mode. The DIS instruction was modified to REPEAT in cycle 1 if the scope is in the erase interval. Since interrupt operations can occur during cycle 1, simultaneous scope erase and data transmission can then be performed.

The availability of Tektronix Type 601 and 611 Storage Display Units prompted the modification of the PC's to allow their use. The longer erase and beam positioning times of the 611 necessitated increasing hardware delays in the PC. The delay circuits had to be modified due to duty cycle instability caused by longer active intervals. Both 601 and 611 provide much improved display quality over the modified 564's. Long term stability is also much better.

Several PC's have been relocated to electrically noisy environments and previously undetected electrical power transients and radiated noise have occasionally caused difficulty. A few of the control lines from the Datamaster were found to have a high noise level and to be shifted slightly from nominal MECL logic levels causing a degradation in noise immunity. The logic levels were adjusted by shifting component values and the noise level was reduced by passive filtering.

Occasional hardware difficulties were traced to improper pulse widths in the PC's. This demonstrated the need for a firm specification of pulse widths and a method of verification. An exhaustive survey of the logic prints was conducted and each pulse was specified concerning nominal, minimum, and maximum widths. A test program was written to cause all pulses to be generated for checking with an oscilloscope.

Two new options useful for debugging programs were designed for the Spear PC's, ISTOP and WSTOP. Both are activated by pushing their respective buttons on the console panel and are deactivated by pressing the STOP button.

The ISTOP (Instruction Stop) option will put the computer in EXAM mode when it starts to execute an instruction whose location is specified by the right switches.

The WSTOP (Write Stop) option puts the computer in EXAM mode after a word has been written into the location that is specified by the right switches. This is especially helpful to a programmer when he finds the contents of a certain register being unexplainably changed.

The hardware for ISTOP and WSTOP is contained on a single printed circuit card and includes 7 Motorola MECL II integrated circuits.

A-7. <u>Datamaster</u>

Personnel: A. M. Engebretson, BCL
H. D. Ambos, BCL
J. R. Cox, Jr., BCL
V. W. Gerth, Jr., BCL

Support: FR 00396

The installation of new Datamasters on all PC computers has been completed. Because of head misalignment and speed differences among the original Datamasters, cards recorded on one machine would not work reliably on the others. To improve compatability among Datamasters the following design changes were made on the new units:

1) A new head assembly was used so that azimuth alignment and head pressure could be more carefully controlled.

2) A belt driven capstan assembly was used to minimize differences in capstan speed among units.

3) The stripe delay was increased so that recording begins after the Datamaster card is fully engaged in the pinch roller assembly.

4) The card guides were polished to minimize frictional drag on the card.

A-8. Interface and Programs for an Inexpensive Fast Printer

Personnel: G. M. Roa, BCL
V. W. Gerth, Jr., BCL

Support: FR 00396

Interfaces to link PC's (both prototype and Spear versions) to a Motorola TP-4000 four line per second printer were designed and installed. The Spear PC version is contained on a single circuit card using 16 MECL II integrated circuits and 9 transistors; the other is made up of 17 DEC Flip Chip cards. Both interfaces contain two program selectable timing systems, one for printing 80 characters per line and the other for 120 characters per line. The latter is useful for reproducing certain IBM printer formats.

A subroutine was written to enable a PC programmer to conveniently use the printer. Upper or lower case characters can be requested by jumping to the printer subroutine with the proper ASCII character code. The subroutine accepts and stores characters until a full line is received, it then prints the line automatically. The next line of characters is accepted while the printer is in operation. The subroutine itself occupies 324_8 locations and the accompanying character patterns occupy 440_8 locations. Space must also be provided for two character code buffers.

B. Computer Applications in Radiation Treatment Planning

Programming support for the radiation treatment planning project diminished during the year while evaluation of both programs and equipment proceeded at the participating institutions (see PR 2, E-1).

Visits to each of these institutions were made for the purpose of installing engineering modifications (see A-6), the new Datamaster (see A-7), improving and calibrating the Rho-theta transducer (see PR 4, A-5) and demonstrating the program DIGIT (see PR 4, B-5). Some improvements were made in existing programs, but major activity focused on a system for measuring the dosage from radiation sources.

B-1. Superimpose Beams Program

Personnel: W. F. Holmes, BCL
A. M. Engebretson, BCL

Support: FR 00396

Revisions were completed (PR 4, B-1) late in the summer of 1968. The program has had extensive clinical use since that time. When the improved Datamaster was installed new Datamaster cards were required (see A-7). The opportunity was used to include a small revision that improves the appearance of isodose lines at the cutoff point near the patient surface. The accuracy was unaffected. The program appears to have sufficient accuracy, speed, completeness, and ease of use for routine clinical practice.

W. F. Holmes, "External Beam Treatment Planning with the Programmed Console," submitted for publication. (BCL Monograph 113)

B-2. Enter Doses

Personnel: E. Van Patten, BCL

Support: FR 00396

The Enter Doses program prepares beam cards from data typed on the PC keyboard. The original version (see PR 3, B-5) has been rewritten to give flexibility to the grid organization. From 2 to 24 depth lines may be combined with an odd number, between 3 and 33, of fan lines, subject only to the restriction that the number of intersections of the fan and depth lines be less than 233. The depth lines have a constant interval, but the fan lines may vary.

The program will also supply the right half of a symmetrical beam from the typed in left half; and it will produce a mirror image of a given beam card.

Incremental plotter routines have also been incorporated making it possible to produce hard copy records of beams and grids. A revised description of the program has been issued (BCL Monograph 105).

B-3. System for Measuring the Dosage from Sources Used in Radiation Therapy

Personnel: A. L. Bodicky, BCL
W. V. Glenn, Jr., BCL
A. Feldman, Ph.D., Radiology

Support: FR 00396
CA 10435

A system has been developed for measuring the dosage produced by individual sources, with or without modification to their fields and with the option to carry out these measurements either in air or water. The sources at the Mallinckrodt Institute of Radiology are: cobalt (Picker), cobalt (Eldorado), and electron accelerator (Allis Chalmers). Each can be accomodated by the system.

The system, called GORTH (Ground Oriented Radiation Tracking Hypsograph), has three major features: 1) a scanner carrying a radiation probe, 2) a variety of orientations of the scanner relative to the beam, and 3) portability of the entire system. The scanner covers a 50 cm. by 50 cm. area with an incremental resolution of .25 mm and a maximum scan rate of 350 increments per second for each axis. The scanner operates identically and in parallel with a commercial incremental plotter.

Two variations of orientation are available when the scanner is horizontal: 1) with source axis entering from side of a water cube (coincident or parallel with scanner plane) or 2) with source axis entering from the top of the water cube without passing through the walls of the cube and perpendicular to the scanner plane. When the scanner is vertical two options are also available: 1) with source entering the side of water cube coincident or parallel with the scanner plane, 2) with source axis entering from top of the water cube and with the source axis coincident or parallel to the scanner plane.

The scanner can be fitted with either a semiconductor diode detector or an ion-chamber and a commercial picoammeter whose output is connected to an analog channel of a digital computer. The intensity of the scanner probe signal is normalized by a second probe placed at a fixed position in the water cube. Data processing and scanner control is accomplished by the Programmed Console (see B-4).

B-4. TUB

Personnel: W. V. Glenn, Jr., BCL

Support: FR 00396

TUB is a PC program which drives a radiation detector through a field of ionizing radiation, measures doses at certain points, and produces a beam card for use in Superimpose Beams.

The pilot study for direct measurement of beam card doses (see PR 4, B-6) was promising enough to warrant design and construction of the special purpose scanner (see B-3).

The general approach in TUB is to generate and display, an appropriate grid (see PR 4, B-5 and B-6) on the storage oscilloscope and then make dose measurements by driving a radiation detector to the point in the radiation field that corresponds to each grid point displayed. Specification of depth interval, depth of J=0 line, fan line positions, or the total number of grid points is quite flexible. Two preliminary scans across the beam at variable depths below the base line provide crossplots of the beam's intensity by displaying these crossplots on the oscilloscope the user may estimate the best position for the fan lines. A reference detector may be positioned under control of console knobs while the detector's position in the beam is displayed on the oscilloscope. A horizontal line whose vertical position represents the detector's voltage is simultaneously displayed. There are options for plotting the grid and/or isodose lines on the digital plotter. Standard or mirror image beam cards may be written with the Datamaster.

C. Cardiac Research

This section contains several reports concerned with the application of computers to cardiology. Much of this work has been aided substantially by scientific collaboration and financial support from other departments at the Medical School. Some new collaborative efforts with Methodist Hospital, Houston, are included here since the primary emphasis is on monitoring during and after cardiovascular surgery.

C-1. Design of a Coronary Care Unit Monitoring System

Personnel: G. Wolff, M.D., Medicine
G. C. Oliver, M.D., Medicine
F. M. Nolle, BCL
J. R. Cox, Jr., BCL
E. Massie, M.D., Barnes Hospital
A. Vose, R.N., Barnes Hospital
J. Jeffers, R.N., Barnes Hospital
J. Burgess, Electronic Shop

Support: FR 00396
HE 11034
Washington University
Barnes Hospital

In the fall of 1968, Barnes Hospital initiated plans for construction of a 15-bed coronary care unit (CCU). While a developmental computer monitoring system is to be an integral part of the unit, a full complement of more conventional patient monitoring equipment is necessary to provide adequate care facilities for all patients. Accordingly, a collaborative effort was undertaken to design a monitoring system especially suited to the needs of the Barnes CCU and composed of commercially available equipment. Evolution of the monitoring system design proceeded from information based on past experience, visits to some existing CCU's and conferences with representatives of equipment manufacturers. During this time it became apparent that selection of an equipment manufacturer must be based on evaluation of a wide variety of factors.

The following is a partial list of the factors involved in this selection. 1) Completeness of equipment line: availability of all elements now in routine use in many existing CCU's plus other elements currently being installed in the more progressive CCU's. 2) Monitoring system design compatibility: the ability to configure the monitoring elements in a manner consistent with the general system design of the Barnes CCU. In this regard, it became apparent that the final system configuration would be strongly dependent on the particular equipment lines chosen. 3) Equipment performance: assessment of the chances of obtaining satisfactory performance of all of the system elements has been difficult because many manufacturers have recently redesigned equipment to take advantage of advances in electronic technology. 4) Maintenance: much of the modern equipment is modular in some sense and most easily serviced by replacing a defective module with a new or factory-repaired module. However, the existence of local representatives with considerable technical knowledge is desirable in the case of larger elements which cannot be conveniently replaced. Training courses for local technicians are also helpful. Confidence in the fiscal stability of the equipment manufacturer is, of course, an important consideration for long-term maintenance. 5) Other services: the help of technically competent factory personnel in discussing system design is particularly desirable. Training courses for medical personnel are also desirable.

The process of selecting an equipment manufacturer was slow because of the large number of companies active in the monitoring area. The field was narrowed to several manufacturers as a result of 1) many demonstrations by local representatives and factory personnel; 2) a thorough study of all monitoring exhibits at the annual meeting of the American Heart Association in November, 1968; 3) conversations with users of various brands in existing CCU's; and 4) detailed analysis of factory supplied schematics. The final choice was weighted heavily by considerations of compatibility with the monitoring system design.

The new Barnes CCU will occupy the eighth floor of the Rand-Johnson building. It is physically segmented into a six-bed, acute unit occupying the south wing and a nine-bed, graduated care unit occupying the north corridor. Although the two units have been designated as Acute and Graduated, no such distinction presently exists in the monitoring equipment capability. Wall-shelf mounted equipment at each bedside contains an ECG amplifier, heart rate meter with high and low alarm limits, dual channel oscilloscope, and one or two optional blood pressure modules which may measure systolic, diastolic, or mean pressure via internal catheter. At the center of the six-bed unit two separate consoles contain monitoring equipment. The nurse's console contains a 19-inch, multi-trace oscilloscope for display of patient ECG's. A set of status lights for each patient conveys to the nurse information about heart rate alarms, ECG lead fault, and standby operation. Each ECG is recorded on a short duration tape-loop. ECG paper records may be obtained at the nurses' console on demand or in event of an alarm. A separate console called a discussion station is available to physicians to review the status of any patient in the acute area. This discussion station contains a dual channel oscilloscope, paper recorder, a blood pressure indicator slaved to the bedside meter, and a patient selector switch. Two ceiling mounted 19-inch oscilloscopes are slaved to the 19-inch oscilloscope in the nurses' console. The nine-bed unit contains similar consoles with the exception that the nurses'console is a dual replica of the nurses' console in the acute unit, dividing the graduated unit into four-bed and five-bed subunits. The Barnes CCU is presently under construction and is expected to begin operation in September, 1969.

C-2. Development of a Digital Computer System for Monitoring Electrocardiographic Rhythms

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Support: FR 00396
HE 11034
Washington University

The new Cardiac Care Unit presently under construction by Barnes Hospital (see C-1) includes a room with 350 square feet of floor space specifically designed for computer monitoring activities. This development has spurred the design and construction of a complete digital computer monitoring system (BCL Monograph 82). Consideration of the high data rates of the ECG and other physiological signals obtained from each patient has led us to an approach which assigns a small digital computer to each patient to be monitored. Each of these dedicated Patient Computers continuously monitors the ECG rhythm of its patient, producing highly condensed output data streams describing the ECG rhythm in different levels of detail (see C-3). Although each Patient Computer is capable of effective ECG rhythm monitoring activity while operating as a stand-alone machine, its capabilities should be enhanced considerably when embedded in a digital computer system which provides fast access to programs, convenient mass data storage and retrieval, and further data manipulation and processing by research investigators. The elements of this system are outlined in the following paragraphs.

Program Broadcast (see C-4) - this system is to provide rapid access to programs for all Patient Computers. In addition to providing the sections of the ECG rhythm monitoring program which must remain resident (e.g., AZTEC and Primitive), the program broadcast should allow overlay of low repetition rate sections (Cycle, Sequence, etc.) expanding Patient Computer capability to higher data analysis levels and versatile textual and data display formats. Dual broadcast channels allow developmental program testing to proceed concurrently with operational programs.

Data Storage - this system is to provide mass storage for the condensed data streams emanating from the Patient Computers. The initial system is composed of a PDP-8L to serve as a data buffer and controller for two Data Disc 7206 magnetic disc memories with a storage capacity of

12.8 megabits. Each Patient Computer will be able to transfer under program control low data-rate streams to the PDP-8L for storage in one or more circular buffer areas on the discs.

Inquiry Computer - the LINC-8 computer (see PR 4, C-4) is to be used on a scheduled basis for further data manipulation and long-term storage on LINC tape. Bidirectional data-transfer channels between the LINC-8 and the disc data-storage system allow interrogation of patient files and the creation of additional files. It is expected that this versatile computer will prove useful for special purpose research investigations as well as routine archival storage.

Patient Computers - initially, two specially modified Programmed Consoles will be used as dedicated patient monitors. Each of these prototype PC's will have a hardware sample instruction, a program broadcast receiver, and a twelve bit parallel data output. A Tektronix 4501 scan converter provides storage oscilloscope display with remote video monitor display at each of the discussion stations in the CCU. The LINC-8 may also be used at scheduled periods of the day as a Patient Computer. This capability may be useful for testing programs to monitor other variables as well as ECG rhythm.

Analog Recording - two reconditioned Ampex FR-100A tape recorders will provide analog recording capability for program debugging and evaluation. These recorders will alternate in operation to continuously record 14 patient ECG's along with the time of day as given every five seconds by an Audichron SA time announcer. The idle recorder will be used for playback of selected episodes. The twelve hours of information on each tape reel will be erased for reuse after several days thus effectively creating a circular analog data buffer of several days duration. An additional benefit is the three second time delay between the record and reproduce heads. We are presently using this feature to obtain a triggered paper chart writeout of the delayed ECG to evaluate premature ventricular contraction detection algorithms.

C-3. Processing Algorithms for Electrocardiographic Rhythm Monitoring

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Support: FR 00396
HE 11034
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The work on processing algorithms for electrocardiographic rhythm monitoring has proceeded under three major headings: development, evaluation and description.

Development - The Primitive Processor program has been rewritten using subroutines which reduce the total program area considerably. Data Storage buffers for the Atrial and Ventricular AZTEC have also been reduced drastically. The Sample, AZTEC, and Primitive Processors along with their data storage areas now occupy less than 2K memory locations in the Programmed Console. Further development of the Cycle and Sequence Processors has been delayed due to the higher priority of work on the system hardware design. However, several special purpose programs have been implemented on the LINC-8, PC combination in order to provide clinically useful data.

One program provides oscilloscope and incremental plotter output of two-dimensional histograms based on Primitive Processor output data. These have most frequently been histograms of QRS duration versus QQ interval, giving a concise, qualitative picture of the number of premature ventricular contractions (PVC's) and the number of normally conducted beats occurring over an interval typically 30 minutes in duration. A serial set of these histograms has provided qualitative information on the effects of antiarrhythmic drug therapy. A second program categorizes each QRS complex as being a PVC or a normally conducted beat. In this program, a PVC is a QRS complex with duration greater than some constant value (usually 110 msec) and with QQ interval shorter than some fraction (usually seven-eighths) of an average QQ interval computed from previous QQ intervals for non-PVC's. A storage oscilloscope display (see C-5) gives the number of PVC's occurring during the last minute and the number of PVC's per minute plotted as a fraction of time over the last two hours and the last 24 hours. This display also provides a plot of percentage data lost (computer recognized artifact, standby operation, etc.) for detecting some unreliable regions in the PVC data plot. This display has been used clinically via a coaxial cable to a video monitor in the present CCU.

Evaluation - A thorough evaluation of the rhythm processor algorithms is difficult because of the wide variety of ECG waveforms encountered in patients in a CCU. We have, wherever possible, worked with on-line signals in order to avoid biasing results to a tape recorded library. A fair degree of confidence in the QRS recognition algorithm of the Primitive Processor has been gained through oscilloscope observation over the past several years of false positives and false negatives. A variety of programs have been used to reconstruct the ECG from the output data of each processor level, showing that information necessary for rhythm monitoring has been retained. Recently, efforts to obtain quantitative information have been initiated. The PVC detection program (see C-5) has been monitored visually for periods of about one hour on patients having PVC's primarily to gather data on the frequency of occurrence and the nature of false negatives. The same program, using triggered paper write-out of the ECG delayed by three seconds, has been used for periods of twelve hours or more on patients having infrequent or no PVC's, to gather data on the occurrence of false positives.

The technique of using one computer (the LINC-8) to monitor the performance of another computer (the PC) has been used to gauge the PC's performance in terms of processor time used and the amount of data reduction accomplished. Measurements of output data rate for each processor are useful in determining the amount of circular buffer storage needed. Measurement of the distribution of processing time used by each processor is helpful in determining the chances of operating in real-time under worst case conditions.

Description - While the ECG rhythm processing programs must necessarily be coded in machine language, our experience has shown a need for an accurate, compact description in a higher level language. For example, inadequate description of the intricacies of the Primitive Processor algorithm for finding the boundaries of the QRS complex has, in the past, hindered internal discussion among people who were familiar with the algorithm. This problem has been alleviated by the development of a language which describes the data output of each processor as a string of symbols. Each output symbol is defined in terms of a string consisting of symbols produced by subprocessors. For example, a "ventricular complex" is composed of optional "Q-wave" elements followed by an "R wave" followed by optional "S wave" elements. These elements are defined in terms of other subprocessor symbols or output symbols of the previous processor. Additional compactness is achieved by the use of recursive definitions where possible. A description of the descriptive language and items mentioned in the section on evaluation have been published.(1)

The manner in which the rhythm processors share the time of a single digital computer has been reported.(2) Each processor is called into operation on a regularly scheduled basis, using computing time available when higher priority processors are not operating. In order to operate in real-time, each processor must be finished before it is called into operation again. Measurements of processor operating time distributions suggest that that technique may be extended to processors which are called into operation on a daily or even less frequent basis.

(1) Cox, Jr., J. R., et al, "Some Data Transformation Useful in Electrocardiography," Computers in Biomedical Research, Vol. III, Eds. Waxman and Stacy, Academic Press, Inc., in press. (BCL Monograph 83).
(2) Nolle, F. M. and Cox, Jr., J. R., "How to Keep Up With the ECG," presented at the IEEE Computer Group Conference, June 19, 1969. (BCL Monograph 124).

C-4. A Broadcast Information System for Cardiac Monitoring

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Support: FR 00396
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The concept of "broadcasting" fixed programs or data from a central "transmitter" simultaneously to any number of "receivers" which carry out computations was conceived by W. A. Clark and C. E. Molnar.(1) An application of this concept to a cardiac monitoring system was initiated during the past year.

A transmitter design has been implemented which provides two broadcast channels, each with a capacity of 16,384 twelve-bit words per broadcast cycle. The transmitter utilizes core memories as the storage element. An interface is provided to allow loading and checking the broadcast memory from the LINC-8 Inquiry Station. The transmitter provides a serial digital output at 3 megabits per second. Word parity is calculated and inserted in the output data stream by the transmitter. The output is formatted in 64 word packets of "blocks" of information. Each block has a unique identifier to enable the receiver to extract a specified portion of the broadcast. Bit timing and block timing are also supplied by the transmitter to the receivers. Standard digital transmission techniques over wide-band cables are used for the distribution of the transmitter outputs to the receivers.

The receiver accepts a block identifier and the number of consecutive blocks (1-7) upon command from a patient computer (presently a Programmed Console). Upon location of the requested information in the broadcast stream, the data is "burst" transferred at memory cycle rates into the overlay area in the patient computers core memory.

The transmitter and receiver are assembled and have undergone preliminary tests. Receiver interfaces for the LINC-8 and Programmed Consoles are presently in the developmental phase.

(1) Clark, W. A. and Molnar, C. E., Computer Systems Laboratory Technical Memorandum No. 61, May 24, 1968.

C-5. PVC Rate Display Program

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Support: FR 00396
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A program has been written and is being tested which detects the occurrence of premature ventricular contractions in a monitored electrocardiogram and calculates the PVC rate. This and additional information are displayed in a clinically useful form.

The program runs on the LINC-8 computer (see PR 4, C-4) and uses data generated and transmitted by ECG preprocessing programs (see PR 2, A-6; PR 3, A-1; and PR 4, C-4) running in a Programmed Console (PC). All ECG input information is from the PC, and all other information is from an on-line teletype. Output for immediate use is displayed on a storage oscilloscope and for future use is written on magnetic tape.

The ECG input consists of interval and duration information on both the QRS complex and the P wave. Using this information, the program classifies each beat as PVC or non-PVC, and keeps track of real time. A detailed graph of PVC rate versus time for the last two hours and a similar graph of the last twenty-four hours is generated on the oscilloscope and refreshed once a minute. Also included in the display are time, date, and rate during the previous minute in digital form, and the patient's name. The interval, duration and classification of each beat are recorded on magnetic tape with date and time inserted every minute so that a portion of the data may be reviewed at a later time if desired. The difference between sixty seconds and the number of seconds of data recorded on tape during a minute is called "lost data" (computer recognized artifact, standby operation, etc.). Graphs similar to those for PVC rate display the percentage of all data that is lost.

Teletype input is provided for the nurse and (during development) for altering decision constants. From the teletype there are many options which can be used during real time execution. A standby status in which no ECG data is analyzed may be entered if desired and analysis may be easily resumed when ready. Patient name on the display may be altered. Time and date may be revised although they are maintained by the program once set. Constants in the PVC/non-PVC decision may be altered to allow testing for possibly better values. Data currently being displayed may be cleared to allow for the initialization of the monitoring of another patient. The location at which data is being recorded on tape can be checked to determine the space left on tape. The tape unit in use can be unloaded and recording continued to another unit. The monitoring program may be terminated and control of the machine returned to the operating system.

For use during the evaluation period there is capability of driving a strip recorder to record the PVC detection of the LINC-8, an observer, or disagreement between the two. This allows later study of patterns of interest. A tape recorder delay loop provides the ability to detect a PVC and then create a record after the fact. Detection of each PVC can be indicated within approximately one beat of occurrence. Minute by minute typeout can be made giving time, pulse rate, PVC rate and percentage data lost.

C-6. Processing of the Fetal Electrocardiogram

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Support: FR 00396
HE 09528
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During the past four years, a total of 950 recordings were taken from patients in the Obstetrics Clinic of Washington University School of Medicine. Some of these were on patients on routine visits to the clinic, some on private patients, and some on patients with complicated pregnancies. In the latter class, 53 records represent recordings requested for confirmation of fetal death. The results of the pregnancies for this last group are tabulated below. (The discrepancy in totals is due to two twin pregnancies, resulting in one live birth and one stillborn each). The 19 with unknown results represent patients who received subsequent care other than at St. Louis Maternity Hospital.

Abortions	7
Stillbirths	12
Live	
With known congenital defect	1
Without known congenital defect	16
Unknown result	19
	55

In addition, 44 recordings were made upon request of the attending physician to test for multiple pregnancies. Of the remaining 853 recordings, 162 patients had normal pregnancies and provided 603 recordings, while 55 patients with complicated pregnancies provided 250 recordings. From the latter group, 94 recordings provided readable averaged FECG's from one or both channels (see PR 4, F-1). A total of 706 sets of averaged FECG's were obtained, 546 of which were from simultaneously recorded leads, while the remaining 160 were from single leads. Final evaluation of all averaged FECG's has not been completed. Of the 162 normal patients, 104 had at least one successful recording and of the 55 patients with complications 39 had at least one successful recording. For the normals there were 20 successful recordings from 60 patients who had only a single recording session and 2 successful recordings from 12 patients with complications.

Thus more than 83 percent of the patients with multiple recordings had at least one success. A test of the efficacy of an optimum processor for the fetal electrocardiogram (see PR 4, F-2) in handling clinical records has been postponed until evaluation is complete for the results of the present processing technique.

Some preliminary efforts toward implementation of the optimum processor have been taken. A "noise whitening" filter is required to transform the FECG plus colored noise to the sum of a modified FECG and white noise. The design of the whitening filter uses the autocovariance function of the colored noise component of the clinical records. Three populations were used to develop a sample covariance function. The first consisted of portions of clinical records in which no fetal activity could be detected visually. The second population was composed of intervals of clinical data which were bounded by detectable FECG complexes. The final group contained samples of records from which a weighted average of the FECG had been subtracted. The samples taken from this last group were not synchronized to the occurrence of the FECG. Epochs of noise from each of these populations were used in approximately equal numbers to compute the sample autocovariance function. Sixteen autocovariance functions were generated for each data record chosen. These were arithmetically averaged. Seventy-six averaged autocovariance functions were thus generated and the grand average of these determined a sample autocovariance for the abdominal noise source. The next step in the design of the whitening filter would be determination of the transformation which converts this autocovariance function to a delta function. Following development of the whitening filter all clinical records must be transformed by this filter to prepare the data for the optimum processor. Next, the eigenvectors of the transformed signal process (FECG) must be computed by operating on each sample member with the whitening filter. Subsequent processing results with the optimum filter would be compared to the corresponding performance of a threshold crossing detector which has been used routinely in the past (see PR 4, F-1).

C-7. <u>Design of a Digital Computer System for Monitoring in an Operating Room and Intensive Care Unit</u>

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Support: HE 05435
FR 00396
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The need to improve the care of critically ill patients, particularly those who are undergoing or have recently undergone extensive cardiovascular surgery, is recognized by those charged with delivering this care. Effective treatment requires thorough knowledge of the physiologic state of those patients. The tasks involved in monitoring their status vary from routine to highly deductive. Highly skilled personnel, in particular specially trained intensive care nurses, presently perform these functions. It may be possible through the use of digital computers to relieve these skilled personnel of the more routine tasks and, by presenting physiologic data in a more easily assimilated form, make more efficient use of their deductive abilities.

Several institutions have attempted to incorporate digital computers into an intensive care facility. Most of these have chosen to use a large central computer to which are attached a number of remote terminals. One or more of these remote terminals is used to serve each patient. Computational time is shared among the remote terminals according to various polling algorithms. It is inevitable with such a system that events occurring during intervals when the remote terminal is not selected go undetected by the monitoring programs. The system designed for installation at the Methodist Hospital in Houston, Texas, proposes to eliminate missed events by providing uninterrupted monitoring for each patient. The system proposed has a number of features which differ from the time-shared scheme described above. Foremost among these is the use of a number of small computers called preprocessors, each dedicated to a single patient. This is economically feasible since these small machines are primarily required to do data manipulation rather than arithmetic and so do not need the costly hardware features found in most large machines. A wide range of monitoring tasks can be performed by these preprocessors operating independently of any other machine. Characteristics of the preprocessors include analog-to-digital conversion capability, a display system for data presentation to the user and several channels for user interaction with the system. More extensive analyses will be performed at a second level in a hierarchy of machines. Data from the patient preprocessors will be transmitted to an "Inquiry Station" for storage and output. Both graphic and alphanumeric presentations will be available.

No executive or supervisor operating system is required to control communication between various levels in the hierarchy since digital data will be exchanged via direct memory access channels. "Hard copy" of data in summary form may be produced on a scheduled basis or upon request. Preliminary plans for production of data in a form compatible with the requirements of large computation centers will permit statistical analyses to be performed in the future.

Development of the system for Methodist Hospital will proceed in two phases under a contract from the Health Services and Mental Health Administration through its Health Care Technology Program. The first phase provides for development of a prototype system serving one operating room and one bed of the intensive care unit. During this first phase, ECG rhythm-monitoring programs developed at BCL will be implemented on the PDP-12 computers chosen for the project. In addition, analysis of the aortic pressure pulse to provide stroke volume and cardiac output, systolic, diastolic and mean pressures, peripheral resistance and a cardiac contractility index is planned. Other variables which may be monitored during the prototype phase are mean central venous pressure and temperature. The second phase of the development will increase the number of beds and operating rooms to six and two respectively and expand the physiologic variable set to include blood gases, respiratory mechanical parameters, respiratory gases and fluid balance. During this phase, a broadcast system for distribution of monitoring programs and data will be installed.

C-8. Design and Installation of a Computer System for a Cardiac Catheterization Laboratory

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Support: FR 00396
HE 11034
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The cardiac catheterization laboratory and its associated computer system are located in two adjacent rooms on the third floor of Mallinckrodt Institute of Radiology. About 75 square feet of floor space was made available for installation of the computer equipment. A viewing window for visual communication was installed in the wall which separates the two rooms and a conduit was installed to allow signal cable to pass from the catheterization laboratory to the computer area. Two-way voice communication via an intercom was also provided.

The two major components of the computer system are a Honeywell signal conditioning and recording system in the catheterization laboratory and a Spear Programmed Console in the computer area. The Honeywell system consists of three channels for blood pressure measurement, two channels for monitoring the ECG, and four general purpose amplifier channels, one of which is used at the present time for dye curve recording. The first derivative of the signal on one of the pressure channels can also be obtained. The system also contains an eight channel monitor and a light beam oscillographic recorder.

The Spear PC as assembled for this installation, consists of the processing and memory unit, a Datamaster unit, a storage oscilloscope, an IBM 360/50 communications unit (see E-1), and a Houston Instrument COMPLOT digital plotter. A special buffer amplifier package was designed and constructed so that signals produced by the Honeywell system have the proper range for the Spear PC analog inputs. The computer operator can select one of several incoming signals for each of the PC analog inputs.

A hardware sample clock was designed and installed on the PC. The clock was designed to eliminate the need for programmed timing loops for sampling the analog inputs. It has a basic sampling rate of either 1000 or 500 samples per second, depending upon the position of a jumper on the sample clock logic card.

Design work has been completed on two other items which will be installed presently. Four multiplexer channels will be added. These will be controlled by the instruction SMX 4+v ($0 \leq v \leq 3$). They will be used for sampling the four channels of catheterization data, so that channels 0-3 will be available for other uses. The I-stop, W-stop capability, described elsewhere (A-6) will also be installed.

Future plans call for the replacement of the present Tektronix Type 611 storage oscilloscope with a Tektronix Type 4501 Scan Converter when it becomes available in the fall. This will then allow for a monitor to be placed in the catheterization laboratory so that the physician performing the procedure will be able to observe the collected data and the calculated results displayed by a set of special programs written for the PC (see C-9).

C-9. Cardiac Catheterization Laboratory Software

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Support: FR 00396
HE 11034
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The computer system outlined in the preceding report (C-8) uses a set of special cardiac catheterization programs:

(1) DATA - This program acquires either intravascular pressure tracings (with ECG) or dye dilution curves from the cardiac catheterization laboratory. The data, along with appropriate calibration values and identifying information, is recorded on Datamaster cards for subsequent use in programs (2) and (3). Special function keys allow convenient reassignment of pressure channels or change in sampling rate while the program is in the sampling mode.

(2) Cardiac Output I - This program is in part a PC transcription of previously documented LINC and LINC-8 cardiac output programs (see PR 2, D-10 and PR 4, C-5, respectively). The dye dilution curve and its calibration values are read from Datamaster cards produced by (1). Cursors are placed at (a) injection time, (b) appearance of the dye at the sampling site, and (c) the beginning and (d) the end of that portion of the curve to be used for exponential curve fitting. Calculations include cardiac output, mean transit time, appearance time, and buildup time. An option for multiple exponential curve fitting aids in finding the best portion of the curve upon which cursors (c) and (d) may be placed. The straight line giving a least-squares best fit to the calibration data is displayed on the scope with an option to delete a bad calibration value and repeat all the calculations. The user may save on the digital plotter the dye curve, cursors, exponential fit based on cursors (c) and (d), and the calculations.

(3) Pressure - The intravascular pressure curves and ECG recorded by (1) are read into this program. The program requests certain cursors to be positioned on up to eight successive beats and calculations such as end diastolic pressure, maximum systolic pressure, mean pressure and dicrotic notch pressure are made. Beat by beat calculations, as well as the average values, are displayed on the scope. Systolic ejection period, diastolic filling period, and valve pressure gradient are additional determinations made when simultaneous pressures such as left ventricular and aortic pressure or left ventricular and pulmonary wedge pressure were taken simultaneously by (1). There is an option for plotting the data and average calculations on the digital plotter.

(4) TRACE - This program aids in calculating ventricular volume from single plane cineangiograms. The approach is to trace with the rho-theta the inner surface of the ventricle, as outlined by contrast media. The program calculates the area of this closed surface and then requests samples of the end points of the ventricle's long axis. Calculations for ventricular volume are based on the work of Sandler and Dodge(1). Quantitation of aortic and mitral regurgitation as well as construction of pressure volume hysteresis loops are the important goals of this program.

(5) Cardiac Output II - This program is under development and will calculate cardiac output from aortic pressure curves based on the work of Warner(2). After a pressure tracing is recorded, cursors are positioned at end diastolic pressure, maximum systolic pressure, and dicrotic notch pressure on up to eight beats. Values of those pressures as well as mean pressure, beat duration, and cardiac output are calculated.

(1) Sandler, H. and Dodge, H. T., "The Use of Single Plane Angiocardiograms for the Calculation of Left Ventricular Volume in Man," Am. Heart J., March 1968, pp. 325-334.
(2) Warner, H. R., "The Role of Computers in Medical Research," J. Am. Medical Assoc., June 1966, pp. 944-949.

D. Computer Applications in Nuclear Medicine

This section contains reports on the application of computers to both dynamic tracer studies and imaging in nuclear medicine. In general we have concentrated on improved temporal resolution rather than spatial resolution. This work has been heavily dependent on our collaboration with the Department of Radiology.

D-1. A Digital Computer System for Processing Data From a Gamma Camera

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Support: FR 00396
AT 01653
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Using the interface described last year (see PR 4, D-1) a system of programs have been written to collect, process, and display data from the Nuclear Chicago Pho-Gamma III camera. Data collection for all experiments is done with a single general purpose PC program. The data is then sent to the IBM 360/50 located on the main campus and stored on magnetic disc for subsequent processing. Requests for processing on the IBM 360/50 are initiated at the PC and results are stored on disk where they can be later retrieved and displayed by the PC.

The general purpose data collection program is capable of collecting forty eight-by-eight arrays of data sequentially in time. The time for each of these arrays is arbitrary and is determined by reading a Datamaster card containing these times from a library of cards previously written. The start of data collection is synchronized by means of a foot switch operated by the person injecting the isotope or timing the experiment. After collection, data is transmitted to the IBM 360/50. With this system, each event from the Gamma Camera is processed by means of the external interrupt feature of the PC. This requires about 50 microseconds per event limiting the system to maximum counting rates of approximately 2000 counts per second. Several experiments are underway using this data collection program.

Regional Cerebral Blood Flow. For this procedure, the computer is set up to record twenty frames of data at 0.5 second each, ten frames at 10 seconds each, and ten frames at 50 seconds each. The collection is started simultaneously with a rapid injection of ^{133}Xe into the internal carotid artery. From the resulting data, blood flow in each of the sixty-four regions is calculated by the method described by Zierler[(1)]

and Lassen[2] (see also PR 4, D-3). The curves of countrate vs. time are displayed along with the value of blood flow in each of the sixty-four regions. Contour lines of equal blood flow plotted over the lateral view of the brain can also be displayed.

Regional Change in Lung Density. For this procedure, a patient stands or sits with his back to the camera face while a uniformly thick sheet of radioisotope, ten millicuries of ^{99m}Tc mixed with water, is placed before him. Each of the forty frames of the PC program are assigned one second times and data collection is started as the patient takes a deep breath. He holds his breath for twenty seconds and then exhales deeply, holding air out of his lungs for the remaining twenty seconds of the procedure. From this data, the change in lung density is calculated in each region by first examining the curve of total counts vs. time for the entire camera face to determine the limits of the inhalation and exhalation portions of the curve. Then this information is used to average counts over each portion of the curve for each of the sixty-four regions. The difference between inhalation and exhalation is calculated and normalized to the mean difference and a contour plot of lines of equal change in density of the lungs is displayed.

Ventilation/Perfusion Ratios. ^{133}Xe is injected intravenously as the subject takes a deep breath. When the concentration of xenon reaches equilibrium, normal breathing is resumed. The slope of the curve of xenon entering the lungs is used as a measure of perfusion of the lungs and the slope of the curve of xenon leaving the lungs after breathing is resumed is used as a measure of ventilation. The ratio of these slopes ventilation/perfusion (V/Q) is calculated regionally and a contour plot of these values is displayed along with time curves of isotope concentration in each of the sixty-four regions.

Region Blood Volume. The change in the distribution of blood in the brain is measured in this procedure. A non-diffusable radioisotope is administered and allowed to reach equilibrium in the blood. Several frames of data are collected and then a bright light shined directly into the subject's eyes. Several frames of data are collected under this new condition and the relative change in blood volume in each area is measured. Contours of equal relative change in volume are plotted along with plots of countrate vs. time in each of the sixty-four regions.

(1) Zierler, K. L., "Equations for Measuring Blood Flow by External Monitoring of Radioisotopes," Circulation Research, Vol. 16, No. 4, April, 1965.
(2) Hoedt-Rasmussen, K., Sveinsdottir, E., and Lassen, N. A., "Regional Cerebral Blood Flow in Man Determined by Intra-Arterial Injection of Radioactive Inert Gas," Circulation Research, Vol. 17, No. 3, March, 1966.

D-2. Display of Static Gamma Camera Images

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

Support: FR 00396

A program has been written to collect a single 32 by 32 array of data from the Gamma Camera and display contour lines of equal isotope concentration. This data can be sent to or retrieved from magnetic disc on the IBM 360/50 and the display offers several options. Individual contours can be selected by the user or alternately a set of contours can be generated by the following scheme. The program searches for the maximum data point in the array, subtracts a user supplied multiple of the square root of the maximum and plots a contour line. Using the value for which the line was plotted, the procedure is repeated until one-tenth of the original maximum is reached.

D-3. The Design of a Six Probe Computer Interface for Studies in Nuclear Medicine

Personnel: R. L. Hill, BCL
N. A. Mullani, BCL
E. J. Potchen, M.D., Radiology

Support: FR 00396
HE 12237

An interface to the PC has been designed and built which will record events from six scintillation detectors (probes). The interface was designed to use much of the existing hardware developed for the interface to the Gamma Camera (see PR 4, D-1). The probes, pulse height analyzers, and coincident circuitry were purchased from Nuclear Chicago Corporation. The six probes can be used separately or as three pairs in coincidence. The pulses from the six probes or three coincidence circuits are prescaled by a factor of 1, 2, 4, 8, 16, or 32 depending on the counting rate of the experiment, and the output of the prescalers go to a six-bit buffer register. This register drives six bits of the external memory address lines of the PC causing a particular memory location to be incremented and the buffer to be reset. The six-bit buffer can be examined and reset every thirty microseconds giving the system an effective maximum rate of over 200,000 counts per second for each probe when its output has been prescaled by a factor of thirty-two.

E. Collaborative Data Processing

The reports presented in this section describe work accomplished toward the implementation of the collaborative modes of operation of the IBM 360/50 with the Programmed Console and the LINC. Our goal is a reliable data processing network with the peripheral computers gathering, preprocessing and displaying data while the IBM 360/50 maintains files and carries out complex numerical processing.

E-1. Switching System for Collaborative Data Processing

Personnel: G. J. Blaine, BCL
H. D. Ambos, BCL
C. R. Buerke, BCL
V. W. Gerth, Jr., BCL

Support: FR 00396

A switching system has been developed and installed to support the collaborative data processing activities of the laboratory and the various stations in the medical center. The collaborative mode of data processing requires the remote terminal, such as the Programmed Console, or LINC, to establish computer-to-computer communication with the Information Processing Center's IBM 360/50 which is located on the main University campus. Full-duplex voice-grade leased telephone lines are used as the communication channels.

The IBM 360/50 is presently equipped with one IBM 2701 Data Adapter Unit. This unit houses two Type III Terminal Adapters which provide two 1200 baud communication channels of the "stop-start" or "asynchronous" type.

The following is a list of remote terminals at BCL and the Mallinckrodt Institute of Radiology (MIR) that are presently using the switching system:

STATION	UNIT	LOCATION
1	Program Development PC	BCL Second Floor
2	Program Development LINC	BCL Second Floor
3	Nuclear Medicine PC	MIR Sixth Floor
4	Data Acquisition LINC	BCL Shop
5	PC Checkout Station	BCL Shop
6	Catheterization Lab PC	MIR Third Floor
7	Radiation Therapy PC	MIR Basement
8	Unassigned	
9	Unassigned	
10	Unassigned	

An additional IBM 2701 with Type III adapters is presently scheduled for installation in August, 1969. This will provide a total of four simultaneous communication channels for collaborative data processing.

The switching system is designed to service up to thirty remote terminals and ten communication channels. The initial installation services up to ten remote terminals, and is modularly expandable in groups of ten. The system assigns a communication channel to the remote terminal on a "first-come, first-served basis." Each remote terminal is provided a control unit. The control unit indicates availability of the communication channels (ALL BUSY or NOT ALL BUSY). If a channel is available the operator can request a channel via a toggle switch. This control unit also indicates a complete connection by detecting the "carrier" signal from the IBM 360/50.

When the collaborative processing has been completed the remote terminal operator disconnects from the communication channel via the toggle switch.

Display panels have been provided in the BCL receptionist's office and on the switching system to indicate which terminals are currently utilizing communication channels.

The principle element of the switching system is a 10 by 10 six-level Cunningham coordinate actuated crossbar. The control logic was implemented with TTL integrated circuits. Resonant reed tone encoders and decoders are used for both control and status signal transmission between the remote terminals and the central switching unit.

E-2. Engineering for Collaborative Data Processing

Personnel: V. W. Gerth, Jr., BCL
H. D. Ambos, BCL
G. J. Blaine, BCL
E. Van Patten, BCL

Support: FR 00396

The previously used interface at the IBM 360/50 between the IBM 2701 Parallel Data Adapters and the Data Transmission Lines to BCL (see PR 3, C-3) has been decommissioned and two Type III adapters have been activated to provide a standard, easily available interface. As before, Ultronic Data Sets and leased lines are used for the three mile path between BCL and the IBM 360/50 at the Information Processing Center.

After installation last year, the Type III adapters functioned satisfactorily until an engineering change was installed by IBM in April. The adapters would not perform correctly in operational programs although all IBM diagnostic tests were passed. BCL provided a Control Unit which allows the two Type III adapters to communicate with each other for tests performed by the IBM Customer Engineer. BCL, in addition, developed a simple echo test program to allow communication with arbitrary constant data patterns.

Testing without the OS/360 environment failed to reveal the difficulty, so a combined effort was mounted involving BCL, Information Processing Center and IBM personnel. It was discovered that the engineering change made the Type III adapter sensitive to the sequence in which channel commands were issued. The difficulty was corrected on an interim basis by disabling the new feature pending a review of the entire situation by IBM.

E-3. Collaborative Data Processing

Personnel: E. Van Patten, BCL
D. A. Bridger, BCL

Support: FR 00396

Implementation of the communications system under the MFT configuration of the operating system (OS/360) has continued throughout the year. Many problems were resolved until a satisfactory level of reliability was reached. In particular the protocol as laid out (see PR 4, E-1) has proven highly successful in providing for error recovery and in preventing the stalemate of two computers listening or sending simultaneously.

Much emphasis has been placed on the development of the IBM 360 programs that respond to requests from PC or LINC terminals. There is a supervisor program and, at present, seven programs to handle specific requests. They are executed in a 12K partition of the IBM 360/50 (the PC-partition), the supervisor being always present, and the others loaded as needed. All are re-entrant and all but one can handle multiple requests concurrently.

The supervisor takes care of all console messages, maintains a log of requests received from the terminals, listens on any idle data lines for requests coming in, analyzes such requests when received, and loads the other programs as needed. Ten requests are now recognized as valid. They are:

GET will send the contents of a member of a file to the remote terminal. Optionally, a specified number of records may be skipped over before transmission begins.

GETL (Get Load) is a specialized version of GET, sending the member LOAD from the PC library file. Its purpose is to allow PC's to start operation after the loading of but one Datamaster card.

GETD (Get Directory) provides the names of all members of any file and the dates of storing. It may also be used to obtain the names of all active files.
PUT will create a new member of a file.
PUTR will replace a member of a file.
PUTP will either put or replace a member.
GTPT is a combination of GET and PUT for editing purposes. After each record of the requested member is sent to the remote terminal, it is returned to the IBM 360, changed if desired, and placed in the new file before the next record is sent. A record may be deleted by returning one of zero length. Records may be added only at the end. The original member is destroyed only if the GET and PUT member names are the same.
DEL will remove member(s) from a file.
CHGE will change the name of an existing member of a file, leaving its contents intact.
RUN will put the contents of a specified file member into the input stream for batch processing in the IBM 360/50. Output from such jobs may be put directly onto disk files for retrieval by the submitting terminal or on any of the available output devices, at the programmer's option. Under release 14 of OS/360 output from SYSOUT (system messages, etc.) was made available to the terminals; however, with the advent of release 15-16 early in the summer, new problems were introduced and this was abandoned temporarily.

Due to the structure of the disk files (partitioned data sets), an attempt to store in two or more members of the same file at the same time will result in scrambling those members. (This is also the reason that RUN may be used by only one terminal at a time). To protect against this, a list is kept of files currently being written on and any of the PUT requests cause this list to be checked.

A two character message is always returned before a request is actually processed to inform the terminal that it can (OK), cannot (NG), or, for PUT, GTPT, or RUN, cannot now (BZ) be complied with.

Seven PC's and LINC's are now connected through an automatic switching system to two data lines connected to the IBM 360. The programs in these computers that utilize the PC-partition must be carefully coordinated with the IBM 360 programs to avoid problems. Subroutines have been written for both computers which do the actual transmission (in either direction) and supply all the details required by the protocol. Each call handles one record only, so that it is the user's problem to make the calls in the proper sequence.

The PC subroutine has been revised and considerably shortened, primarily by deleting some over solicitous error checking which experience has proven unnecessary. In addition, for the PC, a communications monitor has been written to make it easier to use the basic routine. The general utility program (PCUT) has also been expanded to simplify as far as possible manipulations of files that are not necessarily intrinsic to a particular PC program. These routines are all in the final checkout stages. The previous versions having been in operation for some months pointed up some of the areas that needed improvement.

The LINC communications subroutine parallels as closely as possible the operation of the PC routine. It was written originally to allow the PC programmer using the LINC assembler, to conveniently store programs on the IBM 360 disk file for later retrieval by the PC. It may, however, be included in any LINC program which requires communications with the IBM 360.

E-4. General Purpose Programs for Communication Between the IBM 360/50 and the LINC and PC

Personnel: L. K. Berger, BCL
M. Drazen, BCL
W. F. Holmes, BCL
F. C. Rossi, BCL
L. K. Bolef, BCL

Support: FR 00396

A set of programs have been written for routine use of the IBM 360/50 from the LINC and the PC. These routines are oriented toward character strings rather than data, the latter being more appropriate for special purpose machine language programs using the LINC-360 or PC-360 communication subroutines (see E-3). The LINC program (see PR 4, E-3) provides for transfers between LINC tape and the IBM 360 disk files. Both binary and character format can be handled. Character information is stored on LINC tape by LAP6 which provides the ability to type LINC characters line by line, displaying them on the oscilloscope. Lines may be added or deleted anywhere. The entire body of characters can be filed by a name. Thus, the LAP6 system can be used to prepare any character strings acceptable to the IBM 360, such as programs in FORTRAN, PL-1, and assembly language, and data in character format. Similarly, IBM 360 output in character format can be sent to the LINC, and stored as a LAP6 manuscript for subsequent display and listing. Each line of LAP6 manuscript is equivalent to one IBM 360 record. The only restriction is that the set of LINC characters is less extensive than the full range of IBM EBCDIC characters.

The LINC program uses the communication function requests (see E-3), especially PUT, GET, and RUN. The PUT request sends a LAP6 manuscript, or binary information stored sequentially on LINC tape. A manuscript is sent in its entirety, each line as one record, while binary is sent as a selected number of records of fixed but selected length. The sequence of records is stored by the IBM 360 in a file chosen by the user and given a unique file member name by him. The GET request retrieves a file member from the IBM 360, storing it sequentially on LINC tape as a LAP6 manuscript or binary. The RUN request is a simple message specifying file and member names. The records are considered as characters, expanded or sectioned to make up 80 character card images, and inserted into the job input stream normally originating at the IBM 360 card reader. All information for the requests is provided by the users through a "questions and answers" oscilloscope display (see PR 4, F-14).

A listing program has been written for the Motorola printer. Manuscript or binary stored on LINC tape is listed at the rate of four lines per second. The binary is printed in octal form or converted to decimal. The area on tape to be listed is designated by its starting block number, or by its name if filed under the LAP6 system.

A functionally similar PC-360 program called EDIT incorporates a LAP6-like editing system as a basic component. PC characters are typed in line-by-line and displayed on the storage oscilloscope. The number and size of the line is arbitrary, being limited only by the memory buffer available (about 3500 characters). The display can be positioned at any line and additional material inserted or lines deleted. Display size is controlled by the user so that he can have the best viewing conditions for the oscilloscope he is using and his needs of the moment. Numbered columns may be displayed so that standard punch card formats can be readily typed. With the Tektronix 611 storage oscilloscope an 80 character wide field is quite legible. A 120 character field may be used to display full-sized output normally destined for the high speed printer. It is marginally legible, but quite useful for graphs and general orientation, especially since the display can be enlarged at any time.

The entire range of IBM 360 function requests (except GTPT) can be sent merely by typing the request. The PUT request sends whatever the user has typed, each line being sent as one record. GET will accept as much information as the PC can store. In this way programs and data can be retrieved from IBM 360 storage, revised, and sent back again. Output files too large for the PC can be viewed sequentially, with repeated deletes of that already received. Unlike the LINC, the PC program does not handle binary or store information permanently. However, provisions have been made for a Motorola printer listing (see A-8) of IBM 360 file members. The data, either character or binary, comes directly from the IBM 360 with no restriction on number and length of records. Binary is listed as octal or decimal numbers. Characters are formatted as 80 or 120 columns per page. The printer was designed for 80 characters; but the 120 character format is legible, although the characters are compressed in width somewhat. Records too long for one line are continued on the next one.

The LINC program has been used mostly for transmitting data in binary and character form. Binary data is usually created by LINC programs, while much of the character data has derived from punched paper tape read by a paper tape reader interfaced to the LINC (see F-12). The PC version has been generally used for writing short programs, running cataloged programs, and viewing data.

E-5. Graphic Input for Collaborative Data Processing

Personnel: L. K. Berger, BCL
W. F. Holmes, BCL

Support: FR 00396

A simple program has been devised for transmitting graphic information to the IBM 360/50, using the PC with its Rho-theta transducer (see PR 4, A-4 and B-3). The program starts by requesting that the user orient his drawing with the Rho-theta. A new file member is then created in the IBM 360 to receive the graphic records. The spacing between points to be stored is selected (1-9 mm). Line segments can then be traced up to 128 points in length. After checking and possible deletion, each segment is sent as one record to the IBM 360. The data is sent as successive X and Y values in binary quarter millimeter units. There is no limit on the number of records that can be sent. The point spacing may be changed between records.

E-6. Interactive Modeling

Personnel: M. L. Rockoff, BCL
J. Markham, BCL
D. A. Bridger, BCL
J. Mok, Administrative Data Systems

Support: FR 00396
Washington University

We have begun to develop a PC/360 facility for interactively building a mathematical model of a physiological system. We anticipate having a number of general IBM 360 programs available so that an investigator may subject his data to different methods of analysis, including compartmental analysis and nonlinear curve fitting.

An abbreviated version of NIH-SAAM 23 (a simulation and modeling program developed by Dr. Mones Berman, see PR 3, F-5) made available by courtesy of Mrs. M. K. Angell of IBM, was implemented to run under HASP on the IBM 360. The experimental data reside on the disc, as do the associated models; these can be manipulated and the program run from the PC using EDIT (see E-4). Output was retrievable by the PC and could be printed by the Motorola printer. The turn around time for a SAAM run was generally less than 30 minutes, about half of that being used by the Motorola printer.

A general curve fitting program for finding the least squares solution to an overdetermined system of nonlinear equations proposed by Marquardt[(1)] in a version made available by courtesy of Mr. Lloyd Uhler of SUNY at Buffalo has recently been implemented. This program can also be used to solve systems of nonlinear equations.

The problem of determining the "condition" of a nonlinear regression or curve fitting problem is under study and a number expressing the condition can be proposed. It is a function of the model and its parameters only and gives an indication of the amount and kind of data one would need to collect in order to fit the given model and obtain specified accuracy in the parameters. A poorly conditioned problem is one in which it is necessary to determine the observations with utterly unrealistic accuracy in order to compute the parameters with any accuracy at all. For example, a typical model with which we have experimented is such that each datum must have a fractional deviation of less than 10^{-6} in order that the fractional deviation of each computed parameter be less than 10^{-1}.

Fitting data with a linear combination of exponentials is, in general, a poorly conditioned problem. In particular, the model

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

with α_1 close to α_2 (i.e. $\alpha_1 = \alpha_2 + \varepsilon$) is poorly conditioned (unless the data are obtained with fixed percentage accuracy out to very large times). Data generated by such a model can be fit with a single exponential, yet it may be important to an investigator to find out whether his data were in fact generated by more than one exponential. Toward the goal of finding methods of determining the presence of a second exponential, we did some experiments with the almost equivalent model

$$y(t) = (A_1+A_2 - A_1 \varepsilon t)e^{-\alpha_2 t}$$

which is much better conditioned. Our results were inconclusive, due in part to the fact that the curve fitting was done with a straightforward implementation of Newton's method. We have resumed these experiments with Marquardt's method. The few results obtained to date are encouraging.

(1) Marquardt, D. W., "An Algorithm for Least-Squares Estimation of Nonlinear Parameters," J. Society Indust. Appl. Math., 11, 431-441, 1963.

F. Other Applications of Computers

Computer applications that are not described in the previous sections are reported in this section. A few supporting activities are also described. As in many of the preceding sections, much of the work depends upon collaboration with our colleagues. Their names and any associated financial support are listed at the beginning of each report.

F-1. Time Sharing Terminal

Personnel: W. F. Holmes, BCL

Support: FR 00396

A Teletype unit, connected by a dialup telephone line to a General Electric 265 time sharing computer, has been in operation in the Biochemistry Department for the past year (see PR 4, E-5). Limited support has been provided to qualified users as a supplement to the communications system developed between the University's IBM 360/50 and the PC and LINC (see E-1 through E-6). Programs have generally been prepared by research personnel with no previous experience, to aid in their own research work. Most programs were written in BASIC, which is considerably easier to learn than FORTRAN. Since programs can be modified and run again very quickly, most took only a few hours to develop. The principal programs are listed in the following eight reports (see F-2 through F-9).

F-2. Isotope Dispersion of a Molecular Fragment in the Mass Spectrometer

Personnel: W. F. Holmes, BCL
J. Elovson, Ph.D., Biochemistry

Support: FR 00396
Washington University
HE 10406

A molecular fragment in the mass spectrometer need not have the same mass number as another fragment with identical atomic formula, if one of the elements in the fragment has two or more stable isotopes. Thus, a molecular fragment representing a single chemical structure may show peaks at several mass numbers. With larger fragments, the highest peak may no longer have a mass number calculated by assuming only the most abundant isotopes are present. When several elements have stable isotopes, the resulting mass spectrum may be fairly complex, with no clearly dominant mass peak. Interpretation is not easy. A program was written in BASIC to calculate the mass spectrum of an arbitrary fragment, given the isotope weights and abundances, and the number of atoms of each element. The result is plotted as a bar graph by the Teletype. The program was written to solve an identification problem with a silicon derivative of a naturally occurring organic chlorine compound. A match was obtained with one of the trial spectra.

F-3. Tracer Kinetics of Some Compounds Derived from Radioactive Pantothenate

Personnel: J. Elovson, Ph.D., Biochemistry
W. F. Holmes, BCL
G. L. Powell, Ph.D., Biochemistry

Support: FR 00396
Washington University
HE 10406

A radioactive tracer study was made of the formation and turnover of coenzyme A and acyl carrier protein in E. Coli, using externally added radioactive pantothenate. The compounds involved were measured and their specific activity determined. Several types of experiments were performed. Two models seemed plausible based on enzymes known to be present. A program was written to solve the differential equations arising from each model, with a plot of the simulated kinetic curves. One model was consistent with all of the data using the same set of rate constants. The other model could be fit to any one type of experiment, but no set of constants was found consistent with all the experiments.

Paper Submitted:

Powell, G., Elovson, J., and Vagelos, P. R., "Acyl Carrier Protein XI. Synthesis and Turnover of the Prosthetic Group of Acyl Carrier Protein In Vivo." Submitted for publication.

F-4. X-Ray Crystallographic Programs

Personnel: M. Levine, Ph.D., Physiology and Biophysics
F. S. Mathews, Ph.D., Physiology and Biophysics

Support: FR 00396
NSF 57265

The terminal was used for a number of calculations needed for protein structure research, and for developing crystallographic programs to be used ultimately on the IBM 360/50 or on a PDP-8S computer used to control an x-ray diffractometer. The usage includes calculating structure factors for heavy atom derivatives, refining lattice parameters by least squares, and developing programs to reset a misaligned crystal, check Miller indices, and use linear equations to solve the phase problem.

F-5. Effect of Insulin and Trypsin on Transport of Sugar into Muscle

Personnel: H. T. Narahara, M.D., Biochemistry

Support: FR 00396
Washington University
AM 04082

The penetration of 3-0 methyl glucose into muscle was studied in a double labelling experiment, using ^{14}C labelled mannitol and ^{3}H labelled 3-0 methyl glucose. The mannitol was used to measure extracellular water, since it does not pentrate muscle cells. This value was used as a correction to the 3-0 methyl glucose uptake to calculate the intracellular concentration. A computer program was written for routine data reduction. The effect of insulin and trypsin on the kinetics of sugar uptake was studied. Standard errors and confidence limits were established for repeated experiments on individual muscles, using statistical programs devised for this purpose.

Publication:

Weis, L. S. and Narahara, H. T., "Regulation of Cell Membrane Permeability in Skeletal Muscle. I. Action of Insulin and Trypsin on the Transport System for Sugar," Journal of Biological Chemistry, 244, 11, 1969.

F-6. Rate of Sugar Uptake in Shocked Muscle

Personnel: T. Kendrick, Graduate Student, Biochemistry

Support: FR 00396
Washington University
AM 04082

It is possible for leakage to occur into shocked muscle cells, making the apparent rate of sugar uptake to differ from the true rate. In order to correct this, a leakage term must be included in the kinetic equations. A computer program was written to fit the data and derive the true rate of sugar uptake.

F-7. Kinetics of Self Associating Proteins

Personnel: C. Frieden, Ph.D., Biochemistry

Support: FR 00396
Washington University
AM 13332

A number of important enzymes are composed of active monomers into which they can dissociate under a variety of experimental conditions. The association-dissociation reaction may depend on the presence of molecules which occur *in vivo*. Since enzyme activity may change depending on the degree of association, the phenomenon may be an important biochemical regulatory mechanism. A computer model was programmed to study the kinetics of association of an enzyme with four monomers, choosing two mechanisms of association: monomer-dimer-tetramer, and monomer-dimer-trimer-tetramer. The effects of rate constants, equilibrium constants, and external compounds that affect association were studied.

F-8. Kinetics of a Coupling Assay for Phosphofructokinase

Personnel: R. Aaronson, Graduate Student, Biochemistry

Support: FR 00396
Washington University
HE 10406

A phosphofructokinase assay was developed using a multi-enzyme system consisting of phosphofructokinase, aldolase, and alphaglycerophosphate dehydrogenose. The NADH formed by the latter enzyme was measured. Since several enzymes are involved, there is a distinct lag between the time phosphofructokinase is added, and the time NADH begins to appear. A further complication is the activation of phosphofructokinase by its substrate, fructose 1,6 diphosphate. The latter must be carefully controlled to avoid a variable effect on the phosphofructokinase rate. The system's kinetics was simulated with a computer program in order to provide a reasonable theoretical basis for validation of the assay.

F-9. The Formation of Enzyme Substrate Intermediates of the Acyl Coenzyme A Dehydrogenases

Personnel: G. R. Drysdale, Ph.D., Biochemistry

Support: FR 00396
Washington University
CA 10926

The reaction between acyl coenzyme A and its dehydrogenase appears to involve sequential first order reactions with at least three forms of enzyme-substrate intermediate. Experimentally, the reduced enzyme-oxidized substrate intermediate is measured. Deuterated substrates were used in an attempt to isolate the chemical reactions represented by various rate constants in a model mechanism. Data was fit to the model by varying rate constants in a computer program that simulated the kinetics.

F-10. Sodium Transport in the Toad Bladder

Personnel: M. L. Rockoff, BCL
A. L. Finn, M.D., Yale University

Support: FR 00396
AM 10025

Using interactive modeling (see E-6) a mathematical model for sodium transport in the toad bladder is being developed. The experimental apparatus has been described briefly elsewhere(1). The development has required many iterations between computer and experiment. For example, data from some early experiments showed an initial increase in radioactivity on the serosal side of the bladder which was not consistent with any physiologically reasonable model. Using the best available model, the source of the counts was postulated, found and eliminated by changing the experimental apparatus.

SAAM is being used almost exclusively for the analysis of these data, although the serosal data have been subjected to experimentation with Marquardt's method (see E-6) to see if there are two or three exponential terms present.

The current version of the model has two tissue compartments and one chamber compartment each for the mucosal and serosal sides of the bladder. Recognizing that an inherent problem associated with compartmental analysis of data is that many models can be made to fit data from a given experiment equally well, we are seeking the simplest model consistent with a variety of experimental conditions. The present model supports data from the control experiment and for studies with ADH, oubaine, or amphotericin B added to the preparation, and for studies in which the mucosal sodium concentration is altered.

(1) Finn, A. L., "Kinetics of Sodium Transport: Dual Effects of ADH," Abstract, Clinical Research, 17, p. 429 (1969).

F-11. Mass Spectrometer Data Acquisition and Reduction

Personnel: W. F. Holmes, BCL
L. J. West, BCL

Support: FR 00396
Washington University

An LKB 9000 mass spectrometer with a gas chromatographic inlet has recently been acquired by the Biochemistry and Psychiatry Departments. The output from the mass spectrometer is recorded on a high speed oscillograph at rates up to 100 mass unit peaks per second. A large number of records can be produced in one day, due to the speed and resolving power of the gas chromatograph. Yet each record requires several hours for a complete data reduction. A PDP-12 computer has been ordered so that the mass spectrometer can be fully utilized. This computer, a new, modified version of the LINC, will gather the data in real time, partially reduce it, and store the results for further reduction at the investigator's convenience. Final output will consist of a bar graph of mass abundance versus mass number which can be displayed on the oscilloscope, or plotted with a digital plotter.

Program development was begun this summer so that the PDP-12 can be put to use as soon as it arrives. The mass spectrometer output is recorded on the laboratory's Ampex FR-1300 FM recorder. This is then reproduced, and sampled by a LINC, storing the digitized data on LINC tape. Preliminary results show that the raw data can be successfully digitized and stored on LINC tape at real time speeds. Further data reduction can be done off line, without the constraints of operating at a pace forced by the data rate.

F-12. A Paper Tape Reader for the LINC

Personnel: W. F. Holmes, BCL

Support: FR 00396

A Remex RRS302 300 character/second photoelectric paper tape reader was purchased, and an interface designed for the LINC. The reader serves a growing need in the Medical School for a method of converting punched paper tape into a computer usable form. The LINC-reader combination provides a number of possibilities; processing in the LINC, storage on IBM tape or transmission to the IBM 360/50 (see E-4). Through the use of LINC tape as intermediate storage, paper tape data is available to all the LINC's, Micro LINC 300's, and PDP-12's in the Medical School.

Data transmitted to the IBM 360 disc files is available to all computers connected to the computer network - LINC's, PC's and the IBM 360. The reader has been used for conversion of extensive paper tape output from an x-ray diffractometer controlled by a PDP-8S. The data is transmitted to the IBM 360, and processed there. Since the diffractometer can produce a thousand feet of paper tape a day, the equivalent of several thousand punch cards, a large amount of key punching time is saved.

F-13. Pitch Discrimination and Pitch Memory

Personnel: L. Elliott, Ph.D., Central Institute for the Deaf
A. M. Engebretson, BCL
M. D. McDonald, BCL

Support: FR 00396
NB 03856

BCL cooperated with the Central Institute for the Deaf in an effort to produce stimulus tapes for an experiment on pitch discrimination and pitch memory. The experimental design required pairs of short tones to be separated by different frequency intervals (Δf) and different time intervals (Δt). Although only five basic target frequencies were employed (75, 100, 300, 600, and 1200 Hz) a "jitter" of 0, ± 2, ± 4, ± 8 Hz had to be superposed on both the target and comparison frequencies to prevent the listener from learning absolute pitch. In addition, a high frequency signal, generated prior to each stimulus sequence, was to be recorded on the second channel of the two-channel tape recorder. A computer program was written which randomized the experimental conditions and which operated an ensemble of timing equipment, electronic switches, and a voltage-controlled oscillator (all borrowed from the Psychobiology Laboratory), to produce the desired sequence of tones. Although the program performed consistently and accurately, there were difficulties with the tape recorder and with the scheduling of equipment. Work has been continued on a PDP-8S at Central Institute.

F-14. Scanner Systems Software Development

Personnel: J. H. Scandrett, Ph.D., Physics
A. R. Zacher, CSL-BCL

Support: FR 00396
Washington University

The SCOPEMON scanner monitor system (described in PR 4, F-4), has been rewritten in dynamically relocated segments so that when the scanner is called into execution, only the portion of SCOPEMON needed for error recovery resides in core. On termination of a scanner program, SCOPEMON frees all scratch and buffer areas so that the full 45K byte partition of memory is available to the next program.

The new IBM system MFT-II, with multiple input job streams, is now in operation, allowing easier concurrent operation of the scanner-SCOPEMON system while batch computing is in progress and while PC communication is taking place.

A double-buffer paging system has been developed for executing large programs in the 45K byte partition. While page A is executing, page B is being filled from disc with the program modules to be executed next. The system is substantially faster and more efficient than the IBM overlay structure for module replacement.

A text and library handling editor system was developed, based on the IBM 2260 alphameric graphical station. A module of text to be edited (a FORTRAN subroutine, for example) is called into the edit file from a partitioned data set on disc storage. The edit file is a fixed-record length direct access data set. Each line of text becomes an element of a list structure called F. All available empty space in the edit file is in the form of another list structure called E. The two tables of list pointers are held in core, so deletion of text is simply a matter of closing up the F pointer list and adding the deleted record positions to the E pointer list. Likewise, adding a new line (typed on the 2260) involves removing any available record location from the E list, writing the new line in, and adding the record at the desired line number to the F list. Any number of lines may be added or deleted from the text. Entire text modules from the source library may be inserted into the text being edited.

Ten consecutive lines of text are displayed on the 2260. The process of paging forward or backward by any number of lines is made easy by the list structure, which generates the appropriate physical record number, and the direct access method which reads the edit file from disc storage.

The editor also has the capability of sending an edited text, along with appropriate job control text, into the batch partition job stream for compilation or assembly. Also, printer copies or punched card copies of the edit file contents may be obtained by sending the text into the job stream for processing by IBM utility programs. Compiler output can be written on a disc file (again in a list structure) and examined by the editor. With this system, debugging of new programs is greatly facilitated by the short turn around time.

F-15. Tissue Culture Measurements

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

Support: FR 00396
Washington University

Portions of the CELLSCAN system for identity stained leukocytes (see PR 4, F-4) have been adapted for counting and sizing cell colonies. The effects of radiation and chemical treatments on cell reproduction are studied by counting and sizing tissue culture cell colonies grown in Petri dishes. For a feasibility study the stained colonies were photographed on 35 mm film and scanned by an algorithm that first formed a 128 x 128 bit binary core image using a fixed density threshold. A search-and-destory routine called PHAGE then consumed each contiguous group of 1's by an edge-shrinking procedure. Thus the area of each cell colony image was measured. Discrimination of valid colonies from background specks was done by removing the small-area wing of the area histogram. The time required to count and size approximately 100 HeLa cell groups is at present 3-6 seconds, depending on the total area occulted by cellular material.

F-16. Trabecular Spacings on Bone Radiographs

Personnel: S. D. Rockoff, M.D., Radiology
J. H. Scandrett, Ph.D., Physics
A. R. Zacher, CSL-BCL

Support: FR 00396
FR 05389
Washington University

In a previous experiment, at the Jet Propulsion Laboratory, mean trabecular spacings on radiographs of vertebral bodies were determined by digitizing the image with an off-line optical scanner, then processing the image with a computer program which detected vertically oriented trabeculae with a line-seeking digital filter.[1] We are now using our on-line optical scanning facilities for the measurement of the spatial variation of mean trabecular structure along the human distal radius.

In the case of the distal radius, the trabecular structure is more chaotic than that of the vertebra, showing much less tendency toward horizontal and vertical alignment. In addition to measuring the mean trabecular spacing and thickness, we are measuring the angular distribution of the trabeculae relative to the major axis of the bone. We have developed a pattern recognition algorithm (called ARBLIN) which operates on a submatrix of the image and detects the presence of any linear structure, regardless of angular orientation. More specifically, ARBLIN produces for each picture element (which might be an 11 x 11 submatrix of points, for example) one complex output parameter whose magnitude denotes the presence or absence of a density pattern whose gradient changes appreciably along any straight line. The ratio of imaginary part to real part of the parameter reveals the angular orientation of the linear pattern. Thus in one pass over the picture line density and angular distribution are determined.

ARBLIN develops a complex output parameter associated with a point at the center of a picture element by forming a weighted sum of the densities at surrounding points. The ARBLIN algorithm assigns a complex weighting parameter to each point of the surrounding matrix. Consider that the center of the matrix is the origin of the complex plane. The weight value at any point i is $e^{2j\phi i}$, where ϕ_i is the angle of a line segment from point i to the center of the matrix. If a dark line passed through the center and through point i, its trajectory in the complex plane would be $Re^{j\phi i}$. Clearly, then, the point i (and also i' at angle $\pi+\phi_i$) will contribute heavily to the weighted sum when its density is weighted with $(e^{j\phi i})^2$. In contrast, one may see from symmetry that a density field that has a constant gradient will produce a weighted sum that vanishes. Thus, a line gives an output signal which is not only independent of background level but also independent of background density gradient.

Under investigation now are the problems of optimizing ARBLIN parameters in order to remove the effects of x-ray exposure variation.

(1) Rockoff, S. D. and Selzer, R., "Radiographic Trabecular Quantition of Human Lumbar Vertebrae in Situ," III Proceedings of Conference on Progress in Methods of Bone Mineral Measurement, Bethesda, Maryland, February 1968.

F-17. Fourier Boundary Encoding

Personnel: J. H. Scandrett, Ph.D., Physics
A. R. Zacher, CSL-BCL

Support: FR 00396
Washington University

In the differential white cell count, classification decisions between mylocytes, metamylocytes, stabs, and segmented cells are made by trained scanners using subjective human pattern recognition. In implementing a system for automatic typing of stained leukocyte images, the problem arises of quantifying the shape characteristics of cell nuclei which determine their classification. Clearly, some characteristics such as the number of nuclear elements contained within the cytoplasm (one or more than one) are simple to determine. However, characteristics involving cell shapes present difficult problems in computer pattern recognition. For example, the distinction between metamylocytes and stabs depends on the degree of indentation of a kidney bean shape.

A useful Fourier synthesis method for quantitatively expressing object shape has been developed. A closed sequence of points x_i, y_i along the boundary of an object is found by contour following. This boundary is considered as a closed contour in the complex plane $\underline{Z}(S)$, where S is a suitable labelling parameter, such as arc length. The contour is expanded as a Fourier series

$$\underline{Z}(S) = \sum_{n=N}^{+N} \underline{a}_n e^{jnS}$$

where the complex coefficients $\underline{a}_n$ give sizes, proportions and angular orientations of ellipses which go through n complete cycles as S traces points through one complete cycle of $\underline{Z}$. The superposition of these harmonic ellipses can encompass a surprising variety of closed figure shapes with low orders of expansion.

Some obvious advantages of this formalism for expressing shapes include the ease of removing unwanted degrees of freedom, such as translation, rotation and size scale. Thus, general shape factors are easily discerned and tested, independent of positional or angular orientation, and independent of image magnification. Each shape, then, becomes a particular vector in the space of vectors whose components are related to the Fourier components $\underline{a}_n$. For example, a translationally invariant vector is achieved by simply ignoring the two components $\underline{a}_0$ (these are the 0th order cosine series terms for X(S) and Y(S), or in other words, the first positional moments).

We anticipate that Fourier boundary encoding will be a useful pattern recognition tool. For example, a training sample of replications of N object types can be used to generate means and covariance terms for the set of reduced Fourier components. Then the set of coefficients for each object under test generates N identification probabilities, the largest of which indicates the most probable identification.

Fourier boundary encoding has been used to solve the hidden-point problem. The question of whether any point in question is inside or outside an encoded boundary is settled by testing whether the contour Z cycles around the point an even (probably 0) or an odd (probably 1) number of times.

Another possible area of application is the hybrid display system. The coefficients of a contour can be converted from digital to analog form and used to control the relative amplitudes of two sets of harmonic voltage generators driving x and y deflections of a display. Only one cycle time of the fundamental oscillator is required to generate a high resolution closed contour.

F-18. Retinal Cell Dimensions

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

Support: FR 00396
NB 02168
Washington University

Infrared interferometric photomicrographs have been made of single excised frog retinal cells. A timed sequence of pictures shows degenerative dimensional changes(1); rod diameter shrinks and refractive index increases. The objective of the study is a measurement of dimensional and optical changes in rod cells, resulting from a ten second bleaching visible light flux. It is expected that the effects of degeneration can be subtracted from the sudden dimensional change accompanying the bleach.

The cylindrical cells are oriented with their axis transverse to the fringe pattern, and the cell boundaries appear as an abrupt fringe displacement.

An automatic scanning algorithm has been developed for locating the lateral cell boundary. A sample line is stepped through a range of angular orientations and lateral positions, and an edge-strength signal is developed at each trial location. The optimum angle and position is found by peaking the edge-signal. This signal is generated by scanning 50 equally spaced line segments transverse to the test line. A least-squares gradient magnitude estimate is made for each segment and all are averaged, giving a signal proportional to total fringe-shift abruptness. The best test line is found for each side of the cylinder, and midpoint separation is taken as the definition of cell width.

From replications on sample cell images, the sharpness of our edge-strength signal is sufficient to measure cell widths to ~2%.

(1) Enoch, J. M. and Glismann, L. E., "Physical and Optical Changes in Excised Retinal Tissue," Investigative Ophthalmology 5, 208, 1966.

F-19. GRAPHX - A System for the Generation of Graphs Using an Incremental Plotter

Personnel: D. J. Manson, BCL

Support FR 00396

The GRAPHX System operates in conjunction with LAP6 to interpret a graphically oriented language designed to facilitate the plotting of data and creation of figures with an incremental plotter. The initial version previously described (see PR 4, F-15) has been modified and extended to reflect the experience and needs of a variety of users. The language has been extended and made more mnemonic and the memory overlay capability organized in such a way as to allow a user to integrate his own binary data generating or processing programs into data-to-hard copy systems peculiar to his specific needs. As a result relatively sophisticated systems may be controlled through the simple language structure of GRAPHX and personnel unfamiliar with LAP6 programming allowed to accomplish the time consuming tasks of plotting.

Documentation of the system consists of two monographs and a technical report (nearing completion). BCL Monograph 114 entitled GRAPHX describes the use of the System to the user familiar with the LINC and LAP6 programming. BCL Monograph 115 entitled GRAPHX Manuscript Listings includes suggestions and notes for those who wish to modify the system or its subordinate programs. Technical Report #3 entitled GRAPHX System Handbook will instruct the user with no LAP6 programming experience.

F-20. Analysis of Pulmonary Blood Flow as a Function of Cyclic Lung Inflation

Personnel: L. Thomas, M.D., Anesthesiology
A. Roos, M.D., Anesthesiology
D. H. Glaeser, BCL
S. Sutera, Ph.D., Mechanical Engineering
V. Luthra, Graduate Student, Mechanical Engineering

Support: FR 00396
HE 00082

Washington University

The cyclic blood flow response to sinusoidal lung inflation over a wide range of frequencies has been studied under various inflation conditions with a DC perfusion source in excised cat lungs. Appropriate pressure and flow data is recorded on analog tape and then transferred to LINC tape in digital form for analysis, listing and plotting of the results. Analysis includes calculation via Fourier series of the phase relation between the driving function (inflation pressure) and the resultant blood flow as well as lung volume. Total lung compliance and resistance (airway plus tissue) as well as mean vascular conductance are calculated from the above phase relations and the DC and AC amplitudes of inflation pressure, blood flow and lung volume.

Results show that when ventilation is accomplished by cycling airway (tracheal) pressure while keeping all other pressures constant, the blood flow is approximately π radians out of phase with inflation pressure from .05 to 0.8 Hz. On the other hand, when ventilation results from cycling only pleural pressure (pressure around the lung), blood flow at the lowest frequency is either in phase or π radians out of phase but shifts toward $\pi/2$ radians as 0.8 Hz is approached.

These observations have led to the conclusion that the former type of inflation involves a primarily resistive coupling between inflation pressure and blood flow whereas the latter involves a significant capacitive component, assuming small inductive reactance at these low frequencies.

These conclusions have been synthesized with existing knowledge of the physical relations between the air spaces and vasculature of the lung in the form of a simple model of the system which has been solved using analog techniques and found to behave with remarkable similarity to the experimental preparation. Efforts are currently underway to achieve a mathematical solution of the model to facilitate a parametric study of the model via the LINC computer. A manuscript is now in preparation for publication.

F-21. A Linear Model of Microphonic Voltage in the Guinea Pig Cochlea[1]

Personnel: A. M. Engebretson, BCL
J. R. Cox, Jr., BCL
D. H. Eldredge, M.D., Central Institute for the Deaf

Support: FR 00396
NB 03856

A standard experiment used to study the ear is to measure the microphonic voltage generated in the ear for various types of acoustic stimuli. Even though this experiment has been used for over 30 years and has resulted in a better understanding of the ear, theories of cochlear voltage are mainly gross verbal descriptions. In order to determine the relations between the acoustic wave along the cochlea and the microphonic voltage as measured across the cochlea partition, a distributed model of the cochlea was developed. Included in the model are electrical parameters for the membranes, for the fluid, and the hair cells. Measurements of microphonic voltage in the guinea pig cochlea were compared with the results of the model.

The CM model consists of 1) a model of the middle ear, 2) a hydromechanical model of wave propagation in the cochlea, and 3) a distributed electrical model of the fluid, tissue, and hair cells of the cochlea. The middle ear model is a simplified second order system which includes a lumped mass representing the moving parts of the middle ear, the compliance of the ligaments and entrapped air, and the acoustic input impedance of the cochlea. Such a model is a reasonable approximation to the middle ear up to about 4000 Hertz. The hydromechanical model is a transmission line representation of the cochlea in which the parameters that determine wave propagation are compliance and frictional loss of the basilar membrane and the mass of the fluid in the scalae.

The voltage measured by the gross electrodes used in the CM experiments is believed to be a sum of many small voltage sources located in the organ of Corti which are surrounded by conducting fluid and tissue. In order to include the effect of conducting fluid and tissue, a three channel distributed electrical model was developed in which the parameters are impedance per unit length of the fluid in scala vestibuli, scala media, and scala tympani and the admittance per unit length between the scalae and from each scala to ground. The voltages across the membranes in such a model decrease exponentially as a function of distance from the voltage source.

Studies by Bekesy[(2)] and Tasaki, Davis and Eldredge,[(3)] and others indicate that the small voltage generators are located near the potential boundary between scala media and scala tympani. The voltage generators were introduced into the model by inserting current sources across the cochlear partition between scala media and scala tympani. The strength of the current sources were assumed to be proportional to basilar membrane motion.

The theoretical CM voltage was calculated by integrating the contribution of a linear array of such current sources distributed along the cochlea, each driven by the traveling wave displacement at its position. The voltage was computed at three positions along the cochlea corresponding to the three standard electrode positions used in measuring CM in the guinea pig cochlea.

In broad terms, the results of the linear model are in agreement with the measurements in the guinea pig cochlea. The ordering of the theoretical CM curves agrees with the measured curves in that the magnitude at a more apical position is larger and the response falls off at a lower frequency than at a more basal position. The phase relations between turns in the model are also correct over a moderate range of frequencies.

However, a more detailed comparison indicates that certain fundamental differences may exist between the model and the cochlea. These differences occur mainly at low frequencies and involve the phase and slope of the frequency response curves. In addition, it appears that the measured CM voltage is more localized and sharply tuned than the theoretical curves.

The electrical model is probably not at fault since the main feature of the electrical model is to add a voltage spreading effect to the hair cell generators. Voltage attenuation along the model agrees well with measurements of attenuation in the cochlea. To simplify the computation it was assumed that the parameters of the electrical model were constant with respect to position. This assumption will change the magnitude and possibly the cutoff frequency of the theoretical curves, but should not affect the low frequency characteristics.

It is possible that the CM model is incorrect with regard to the role of the hair cell as a CM generator. It was assumed that the hair cell acts like a tiny current source located across the insulating boundary between scala media and scala tympani. The model is oversimplified in this respect because of lack of detailed impedance measurements within the organ of Corti. The organ of Corti no doubt contains several insulating boundaries and fluid-filled passages that should be included in a more complete model.

The details of mechanical coupling between the basilar membrane and the hair cells and the role of the tectorial membrane are not well defined. Bekesy describes the tectorial membrane as having mechanical properties that are frequency dependent. It yields easily at low frequencies but acts like a solid at high frequencies. A frequency dependent property like this might account for features of the CM at low frequencies except that the first turn response is different from the response of the second and third turns.

The most likely source of theoretical error seems to be in the traveling wave model. Unfortunately there are no off-the-shelf theories of hydromechanics that would be a significant improvement over Zwislocki's theory which is the basis of the model used in this study. The three most prominent theories have been developed by Peterson and Bogert,(4) Fletcher,(5) and Zwislocki,(6) and are different only in the choice of parameters used in the wave equation. None of these theories result in traveling waves that have phase characteristics at low frequencies similar to the CM response. A hydromechanical theory developed along different physical considerations has been proposed by Ranke.(7) However, the equations are difficult to solve and a mathematical development of this theory has not been carried far enough to be used as the basis for a traveling wave model. It appears that more should be done on theories of cochlear hydromechanics.

Conclusions that can be drawn from this work are 1) in broad terms, the theory of CM is consistent with measurements of CM in the cochlea, 2) fundamental differences between the CM model and the cochlea at low frequencies suggest that present theories of hydromechanics are inadequate, and 3) more detailed measurements of wave propagation in the cochlea and electrical characteristics of the cochlea are necessary to guide the development of more complete CM models.

(1) Engebretson, A. M., "A Study of the Linear and Nonlinear Characteristics of Microphonic Voltage in the Cochlea," D. Sc. Dissertation, Washington University, St. Louis, Missouri, 1969.
(2) Von Bekesy, C., "Gross Localization of the Place of Origin of the Cochlear Microphonics," Journal of the Acoustical Society of America, 24, pp. 399-409, 1952.
(3) Tasaki, I., Davis, H., and Eldredge, D. H., "Exploration of Cochlear Potentials in Guinea Pig with a Microelectrode," Journal of the Acoustical Society of America, 26, pp. 765-773, 1954.
(4) Peterson, L. C., and Bogert, B. P., "A Dynamical Theory of the Cochlea," Journal of the Acoustical Society of America, 22, pp. 369-381, 1950.
(5) Fletcher, H., "The Dynamics of the Cochlea," Speech and Hearing in Communication, D. Van Nostrand Company, Princeton, New Jersey, pp. 235-259, 1953.
(6) Zwislocki, J., "Analysis of Some Auditory Characteristics," Handbook of Mathematical Psychology, Vol. III, edited by R. Duncan Luce, R. R. Bush, and E. Galanter, J. Wiley and Sons, Inc., New York, 1965.
(7) Ranke, O. F., "Theory of Operation of the Cochlea: A Contribution to the Hydromechanics of the Cochlea," Journal of the Acoustical Society of America, 22, pp. 772-777, 1950.

F-22. <u>Data Processing for a Microspectrophotometer</u>

Personnel: J. M. Enoch, Ph.D., Ophthalmology
L. Brock, Ophthalmology
A. L. Bodicky, BCL

Support: FR 00396
NB 02168
Washington University

A system for the measurement of the transmission of monochromatic light of varying wavelengths through retinal tissue has been described previously (see PR 2, C-4; PR 3, F-1). An option to record digital data on a small portable tape recorder has been added to the system. Thus, experimental data may be stored for later processing. A program for calculating percentage transmission or percentage absorption has been written.

VI. TRAINING ACTIVITIES

During the year BCL engaged in the following training activities:

Course in LINC and PC Programming, September 1968

The course was taught by Michael D. McDonald and included binary arithmetic and coding in both machine language and assembly language.

Attending the course were:

R. W. Bartlett, M.D.	Surgery
Amilia Compas, B.S.	Physiology
Arnold Feldman, Ph.D.	Radiology
Joan Fink, B.A.	Pathology
Everett Flannigan, Ph.D.	Physiology
Irving Gratz, M.S.	Physiology
William Holland, A.B.	Psychiatry
Chim-Chi Kao, B.S.	CSL
Kuo-Chee Liang, B.S.	CSL
Maxine Rockoff, Ph.D.	BCL
Michael Wade, M.S.	Physiology

Course in LINC and PC Programming, February 1969

The course was taught by Michael D. McDonald and included binary arithmetic and coding in both machine language and assembly language.

Attending the course were:

Pat Argos, Ph.D.	Physiology
Jim Baker, B.S.	BCL
Chuck Buerke	BCL
David Camenga, M.D.	Neurology
Robert Druet, M.D.	Surgical Pathology
Martin Feldman, M.D.	Neurology
Susan Holmes, B.S.	Psychiatry
Tom Lustig	Graduate Student
Wanda Meek	BCL
Barry Milder	Medical Student
Stan Mogelson	Graduate Student
Nizar Mullani, B.S.	BCL
Bill Orr, Ph.D.	Psychology

Jim Pexa, B.S.	BCL
Gerald Reed	Radiology
Nikolaus Schad, M.D.	Radiology
Nita Shah, B.S.	Physiology
John Van Gilder, M.D.	Neurosurgery
Gerald Wolff, M.D.	Medicine

VII. PUBLICATIONS

The Biomedical Computer Laboratory has established a monograph series to systematize the many informal reports, reprints, program descriptions and other documents written at BCL or supported by some of the laboratory's facilities or staff. The list of monographs based on reports and articles prepared since the laboratory's inception in April, 1964, now stands at 117. Copies of the index to the BCL monograph series are available on request.

Publications and papers presented during the period covered by this report are listed below. In addition, a few papers now published, but not listed in previous reports are included.

Cox, Jerome R., "Economy of Scale and Specialization in Large Computing Systems," Computer Design, pp. 77-80, November 1968.

Cox, Jerome R. and Medgyesi-Mitschang, Louis N., "An Algorithmic Approach to Signal Estimation Useful in Fetal Electrocardiography," accepted for publication in IEEE Transactions on Bio-Medical Engineering.

Cox, Jerome R., Fozzard, Harry A., Nolle, Floyd M., and Oliver, G. Charles, "Some Data Transformations Useful in Electrocardiography," to be published in Computers in Biomedical Research, Vol. III, Academic Press.

Cox, Jerome R., "Progress Report on the Programmed Console," presented at the Second International Conference on the Use of Computers in Radiation Therapy, September 24-27, 1968.

Cox, Jerome R., "Data Reduction Techniques Useful in ECG Rhythm Analysis," presented at the Workshop on Computers and Electrocardiography, sponsored by Queens University, Kingston, Ontario, Canada, October 3-4, 1968.

Cox, Jerome R., "The Use of Small Computers in Biology and Medicine," presented at the Annual Meeting of the American College of Neuropsychopharmacology, December 18-20, 1968.

Cox, Jerome R., "Interactive Use of Digital Computers in Medicine," presented at the Washington University Conference on Electronics and the Solid State, April 10-11, 1969.

Cox, Jerome R., "Limitations on Data Acqusition in Dynamic Imaging," presented at the Annual Meeting of the Society of Nuclear Medicine, July 23-27, 1969.

Eldredge, D. H. and Engebretson, A. M., "Nonlinear Cochlear Microphonic Potentials," Journal of the Acoustical Society of America, Vol. 45 (305A), 1969.

Engebretson, A. M. and Eldredge, D. H., "Model for the Nonlinear Characteristics of Cochlear Potentials," Journal of the Acoustical Society of America, Vol. 44, No. 2, August 1968.

Engebretson, A. Maynard, "A Study of the Linear and Nonlinear Characteristics of Microphonic Voltage in the Cochlea," Washington University, St. Louis, Missouri, 1969 (D. Sc. Dissertation).

Finn, A. L., "Kinetics of Sodium Transport: Dual Effects of ADH," Abstract, Clinical Research, 17, p. 429 (1969).

Glaeser, Donald H., "Evaluation of Optimum and Sub-Optimum Processors for the Fetal Electrocardiogram," Washington University, St. Louis, Missouri, 1969 (D.Sc. Dissertation).

Hill, R. L., Clifton, J., Gallagher, T. L., and Potchen, E. James, "Regional Cerebral Blood Flow in Man - II. Data Acquisition and Analysis," Archives of Neurology, Vol. 20, pp. 384-387, April 1969.

Holmes, W. F., "External Beam Treatment Planning With the Programmed Console,"accepted for publication in Radiology.

Lien, Monte D., "Digital Communication Over a Noisy, Frequency-Dependent Transmission Line," Washington University, St. Louis, Missouri, 1969 (M.Sc. Dissertation).

Londe, S., Oliver, C. and Nolle, F., "On-Line Computer Estimation of Cardiac Stroke Volume," Surgical Forum, Vol. XIX, pp. 111-113, 1968.

Nolle, Floyd M., "How To Keep Up With the ECG," presented at the 1969 Computer Group Conference sponsored by the Institute of Electrical and Electronics Engineers, Inc., Minneapolis, Minnesota, June 1969.

Potchen, E. James, Bentley, R., Gerth, W., Hill, R. L. and Davis, D. O., "A Means for the Scintigraphic Imaging of Regional Brain Dynamics - Regional Cerebral Blood Flow and Regional Cerebral Blood Volume," International Atomic Energy Agency Symposium on Medical Radioisotope Scintigraphy, Salzburg, Austria, August 6-15, 1968.

Potchen, E. James, Davis, D. O., Wharton, Thomas, Hill, Rex, and Taveras, Juan M., "Regional Cerebral Blood Flow in Man - I. A Study of the Xenon 133 Washout Method," Archives of Neurology, Vol. 20, pp. 378-383, April 1969.

Powell, G. L., Elovson, J., and Vagelos, R. P., "ACYL Carrier Protein - XI. Synthesis and Turnover of the Prosthetic Group of Acyl Carrier Protein *In Vivo**," submitted for publication.

Wies, L. S. and Narahara, H. T., "Regulation of Cell Membrane Permeability in Skeletal Muscle. I. Action of Insulin and Trypsin on the Transport System for Sugar," *Journal of Biological Chemistry*, *244*, 11, 1969.