1966

Progress Report No. 2

Biomedical Computer Laboratory

PROGRESS REPORT

No. 2

August 15, 1966

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

BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

PROGRESS REPORT NO. 2

1 July 1965 - 30 June 1966

TABLE OF CONTENTS

I. INTRODUCTION

The second progress report from the Biomedical Computer Laboratory (BCL) summarizes work done during the period from July 1, 1965 through June 30, 1966. In contrast to the first report which covered a period of 14½ months, this and succeeding reports cover a period of exactly one year.

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 LINC (Laboratory INstrument Computer) or a PC (Programmed Console). In some cases the experimental facilities were brought to BCL. In others the computer was taken to the laboratory. Data has been sent from various laboratories to BCL by analog tape recordings or by phone lines.

A second class of applications requires the use of advanced information-processing techniques. This portion of our research program is conducted within the administrative framework of BCL although extensive use is made of both personnel and facilities of the Washington University Computation Center. The program is directed toward the development and evaluation of new computational methods in support of biomedical research.

A third class of applications requires extensive computational manipulation. These "computational services" aid many investigators in their research through the use of established statistical and information handling procedures. During the past year the work has been carried out entirely on an IBM 7072 at the Washington University Computation Center. Programmers and mathematical analysts have spent most of their time at BCL, but have travelled to the Computation Center to run and debug their programs. Computational services are supported by a variety of sources, the medical school, various grants and contracts held by investigators at the medical school and the Computation Center itself.

On May 1, 1966, the name of the Washington University Computation Center was formally changed to the Washington University Information Processing Center. Since almost all of the period covered by this report preceded the change of name, the older name is used throughout. However, readers should be careful to use the name Washington University Information Processing Center in the future.

On July 1, 1966, the Department of Physiology became the Department of Physiology and Biophysics. However, throughout this report the former name is used.

II. SOURCES OF SUPPORT

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

FR 00161	Biomedical Computer Laboratory Facility
FR 00215	Biomedical Information Processing Research

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

AI 04646	Immunochemical Basis of Penicillin Hypersensitivity
AM 07507	Trace Metal Content of Human Tissues
CA 09741	Biometry of Colonic and Rectal Neoplasms
CA 5139	Training in Radiation Therapy, Physics, and Biology
ES 00139	Center for the Biology of Natural Systems
FR 00218	Computer Technology Center for Biology and Medicine
GM 07176	Cellular Differentiation Induced by Environment
GM 09830	Cellular Regulation of Protein Synthesis
GM 10642	Nucleic Acid Metabolism in Differentiating Tissues
GM 1608	Medical Student Training Grant
HE 00082	Clinical and Experimental Research in Respiration
HE 08507	Pressure, Flow and Impedance Relationships in the Dog
HE 09019	Mechanism of the Heart Beat

HE 09528	LINC Computer Study of the Fetal Electrocardiogram
MH 05806	Behavioral Correlates of Neurophysiological Variables
NB 02168	The Etiology of Reduced Visual Function
NB 03856	Auditory Communication and its Disorders

A National Science Foundation grant, a National Space Agency grant, an IBM contract, and an Advanced Research Projects Agency contract helped to support portions of several projects:

NSF G 22296	Expansion of Computing Center
NASA NsG(t)-86	NASA Training Grant
IBM Contract	Study of Computer Requirements for the Biomedical Sciences
ARPA SD 302	Research for Support of a Program in Macromodular Computer System

Finally, portions of many projects were supported by:

Ellis-Fischel State Cancer Hospital
Mallinckrodt Institute of Radiology
Washington University School of Applied Science and Engineering
Washington University School of Medicine

The sources of support for each of the research projects reported in Section V are listed there. All government support is listed by grant number only.

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.

Research Associates

William E. Ball, Sc.D.*
Richard A. Dammkoehler, M.S.*
Tom S. Gallagher, M.S.
William Holmes, Ph.D.
James M. Vanderplas, Ph.D.*
George S. Whitlow, Jr., B.S.

Research Assistants

Andrew L. Bodicky, B.S., since October 14
A. Maynard Engebretson, M.S.
Ramasami Ganesan, M.S., since June 15
V. William Gerth, Jr., M.S.
Donald H. Glaeser, M.S.
Michael Koenig, M.S.
Daniel J. Landiss, B.S.
Robert G. Loeffel, B.S.*, since October 25
Michael D. McDonald, B.S.
Floyd M. Nolle, B.S.
Elizabeth Van Patten, B.S., since June 13

Programmers

Madhu Bhide, A.B., since November 1
David Bridger, B.S.*
Donald R. Franz, M.S.
Richard M. Hesse, M.S.
J. Philip Miller, A.B.
David Sholtz, B.A.
Kay Shumate, B.S.
Bruce J. Walz, B.S.

Technical Assistant

Clayton Lee Myers, B.S., since June 13

Engineering Assistants

Harry Agress, Jr.
David A. Brown, since June 6
Harry R. Grodsky, B.S.
Ralph S. Mueller, M.S.
David Velten, B.S., since June 6

Programming Assistants

Dale Dierberg, B.A., since June 7
Susan P. Kahn, since June 7
Peter J. Kirwin, since June 6
Peter Payne
Davis M. Swan, B.S., since December 1
Patricia L. Talmage, since June 6
Trilochan Wadhwa, M.S., since June 6

Electronic Technicians

Fred L. Francis
Richard E. Hitchens
Charles E. Mitchell
Kenneth F. Rath,*since June 6

Technical Supervisor

Norman T. Kinch*

Office Clerk

Larry W. Lewis*, since December 21

Secretaries

Brigitte R. Clark*, since June 15
Ruby B. Hoxsey
Janet Litzsinger, since June 27
Wanda J. Meek
Sharon L. Passero*

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

Advisory Committee

The Liaison Committee for the Computer Sciences under the chairmanship of Dr. R. M. Krause served the Biomedical Computer Laboratory in an advisory capacity during the past year.

Harvey R. Butcher, Jr., M.D., Surgery
Donald H. Eldredge, M.D., Central Institute for the Deaf

Herman N. Eisen, M.D., Microbiology
John W. Josse, M.D., Physiology
Richard M. Krause, M.D., Preventive Medicine
Wm. W. Sleator, Jr., Ph.D., Physiology
M. M. Ter-Pogossian, Ph.D., Radiology

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

M. R. Behrer, M.D., Pediatrics
R. I. Berns, B.S., Computation Center
M. W. Brown, M.D., Radiology
D. E. Burlingame, D.Sc., Computation Center
R. Burstein, M.D., OB/GYN
S. L. Clark, M.D., Anatomy
W. A. Clark, B.A., Computer Research Laboratory
R. A. Cook, D.Sc., Computation Center
J. M. Enoch, Ph.D., Ophthalmology
H. A. Fozzard, M.D., Medicine
R. L. Hamblin, Ph.D., Sociology
L. Harth, B.A., Pediatrics
D. C. Hellam, M.D., Medicine
B. Hixon, B.S., Preventive Medicine
G. C. Johns, B.S., Computer Research Laboratory
J. W. Josse, M.D., Microbiology and Physiology
D. E. Kennell, Ph.D., Microbiology
S. P. Londe, M.D., Surgery
G. C. Oliver, M.D., Medicine
A. M. Olson, B.S., Computation Center
L. A. Palmer, M.D., Radiology
C. W. Parker, M.D., Medicine
H. M. Perry, M.D., Medicine
W. E. Powers, M.D., Radiology
A. R. Rawizza, B.S., Computation Center
A. Roos, M.D., Physiology
T. T. Sandel, Ph.D., Computer Research Laboratory
J. H. Satterfield, M.D., Psychiatry
A. I. Sherman, M.D., Obstetrics
W. W. Sleator, Jr., Ph.D., Physiology
S. J. Smith, M.S., Computation Center
L. H. Snow, B.S., Computation Center
J. S. Spratt, Jr., M.D., Surgery
S. C. Stevens, Ph.D., Biochemistry
P. E. Stohr, M.D., Neurosurgery

M. M. Ter-Pogossian, Ph.D., Radiology
L. J. Thomas, M.D., Anesthesiology
M. A. Tinnell, B.A., Pediatrics
R. L. Walton, B.A., Computation Center
W. W. Wayne, M.S., Computation Center
R. B. Woolf, M.D., OB/GYN
R. R. Wright, M.D., Neurology

Central Institute for the Deaf

M. K. Bauer, B.S.
D. H. Eldredge, M.D.
L. L. Elliott, Ph.D.
J. D. Miller, Ph.D.
A. F. Niemoeller, Sc.D.

Ellis-Fischel State Cancer Hospital

A. M. Evans, M.D.

St. Louis University

I. A. Coret, M.D., Pharmacology

St. Louis College of Pharmacy

R. L. Schnaare, Ph.D.

STUDENTS

During the period covered by this report the following students have worked in the laboratory or with laboratory staff members:

M. E. Dodge, B.S., Medical Student
F. S. Letcher, B.A., Medical Student
W. E. Long, B.S., Graduate Student
L. Medgyesi-Mitschang, M.S., Graduate Student

CHANGES IN PERSONNEL

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

Michael Koenig, Research Assistant, on September 3
Daniel T. Landiss, Research Assistant, on September 15
Michael D. McDonald, Research Assistant, on September 14, rehired January 24
Donald R. Franz, Programmer, on June 30
Richard M. Hesse, Programmer, on June 30

Kay Shumate, Programmer, hired July 1, terminated January 1
Bruce J. Walz, Programmer, hired September 13, terminated December 4
Harry Agress, Jr., Engineering Assistant, on September 15, rehired June 6
Harry R. Grodsky, Engineering Assistant, on September 20
Ralph S. Mueller, Engineering Assistant, hired August 24, terminated September 23
Peter Payne, Programming Assistant, hired July 22, terminated September 21
Ruby B. Hoxsey, Secretary, on June 16
Sharon L. Passero, Secretary, on June 15

IV. PHYSICAL RESOURCES

On April 15, 1964, the Biomedical Computer Laboratory was formed and the original staff moved into 5,463 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 the LINC (Laboratory INstrument Computer). This small stored-program computer has been designed specifically for use in the biology and medical laboratory where there is a requirement for strong coupling between the computer, the investigator and other experimental equipment. At that time there were six LINCs in the Washington University Medical community. Three more have been added this year for a total of nine. Two belong to BCL, five to our sister laboratory, the Computer Research Laboratory, one to the Department of Neurology and one to the Central Institute for the Deaf. BCL's computational facilities have also been increased this year by the completion of a pre-production model of the Programmed Console. The Programmed Console has been designed at BCL to function as a combined stored-program digital computer and remote display console for the new IBM 360/50 installed during May, 1966, at the Washington University Computation Center. Other laboratory facilities include a well-stocked electronic shop, a large inventory of electronic and computer test equipment, a variety of digital system modules and tape recorders, both digital and analog.

On August 1, 1964, the laboratory space was increased by an additional 983 square feet on the second floor of the building just south of the original space. Facilities for computational applications are housed in this space. These facilities are in direct communication with the IBM 7072 at the Washington University Computation Center via phone lines and an early prototype of the Programmed Console. During this report period BCL laboratory and office space was increased by an additional 2,406 square feet to a total of 8,852 square feet. This space is also on the second floor of the building just south of the original space. Included in this addition is a classroom that has been used for training activities throughout the year.

V. RESEARCH PROJECTS

A. Laboratory Applications

The following research projects were carried out primarily through the efforts of the laboratory staff members, but often with the collaboration of investigators from other departments. In this section we emphasize laboratory applications in which close coupling between computer, experimenter and experimental apparatus is required.

1. The Programmed Console: An Aid to the Radiologist in Treatment Planning

Personnel: J. R. Cox, Jr., BCL
V. W. Gerth, BCL
D. Velten, BCL
A. L. Bodicky, BCL
G. C. Johns, Computer Research Laboratory

Support: FR 00161
FR 00218

The Programmed Console (PC) has been designed to function as a combined stored-program digital computer and display console which will be useful to the radiologist in treatment planning. The PC can communicate over telephone lines with a larger computer located elsewhere.

The PC operates in either of the following two modes (see Fig. 1):

1) Autonomous mode, as a small independent computer that can aid the radiologist in simple manipulations of isodose contours.
2) Collaborative mode, as a remote terminal participating with a powerful central computer in sophisticated treatment planning.

The computer system (see Fig. 2) consists of a processor, a memory, a keyboard, a storage oscilloscope, a position transducer, a data storage device, and phone line equipment. The processor includes four 12-bit registers and their associated control logic all operating at a two megahertz clock rate. The memory contains 4096 12-bit words of ferrite core storage with a two microsecond cycle time. The keyboard provides a flexible means for interaction between the user and the PC and includes the necessary control push buttons. Also located at the keyboard are four knobs whose position can be sampled by means of four analog input channels. To increase flexibility and reduce cost, the analog-to-digital conversion for each of these channels is accomplished primarily by programming rather than by hardware.

Four jacks on the keyboard provide inputs for four external analog signals. When plugs are inserted in these jacks the corresponding knob is disconnected. One device that may use these inputs is a pen-like position transducer (see A-12). A pen mounted on an extendable arm may be moved easily over a sheet of paper or an X-ray. The radial and angular position of this pen produce proportional voltages which can be sampled by two of the analog input channels.

The principal output device for the PC is a storage oscilloscope with a screen measuring 8 cm by 8 cm and both graphical and alphanumeric information can be displayed. A device for the mass storage of data, the Datamaster, is

connected to the computer through one of eight input-output channels. Binary serial data in exactly the form used for telephone transmission is stored on a strip of quarter-inch magnetic tape fixed to a 3½ inch by 9 inch card. The Datamaster can either read or write up to 256 12-bit words on a single card. A file of such cards can store either programs or data. One special card can be used to provide initial "start-up" routines whenever the PC is turned on.

A switch on the Datamaster causes it to be bypassed and connects the PC to a leased telephone line. Frequency shift keying (FSK) is used to transmit the binary serial data over ordinary voice grade lines. A standard Bell System Data Set (Model 202D) may be connected for the transmission of digital information over ordinary switched telephone networks. Optional equipment such as a Teletype printer or an incremental plotter may also be connected to the PC. (See also A-11, A-12, A-15, A-16, B-9, B-10, E-1).

Papers Presented:

J. R. Cox, Jr., V. W. Gerth, W. F. Holmes, "The Programmed Console: An Aid to the Radiologist in Treatment Planning", Presented at the International Conference on the Use of Computers in Therapeutic Radiology, Cambridge, England, 14-17 June 1966. To be published.

B. Walz, V. W. Gerth, W. E. Powers, J. R. Cox, Jr., T. L. Gallagher, "A Small Computer (Programmed Console) for Radiation Dosimetry Calculations", Presented at the 14th Annual Meeting Association of University Radiologists, May 12th-14th, 1966, Little Rock, Arkansas.

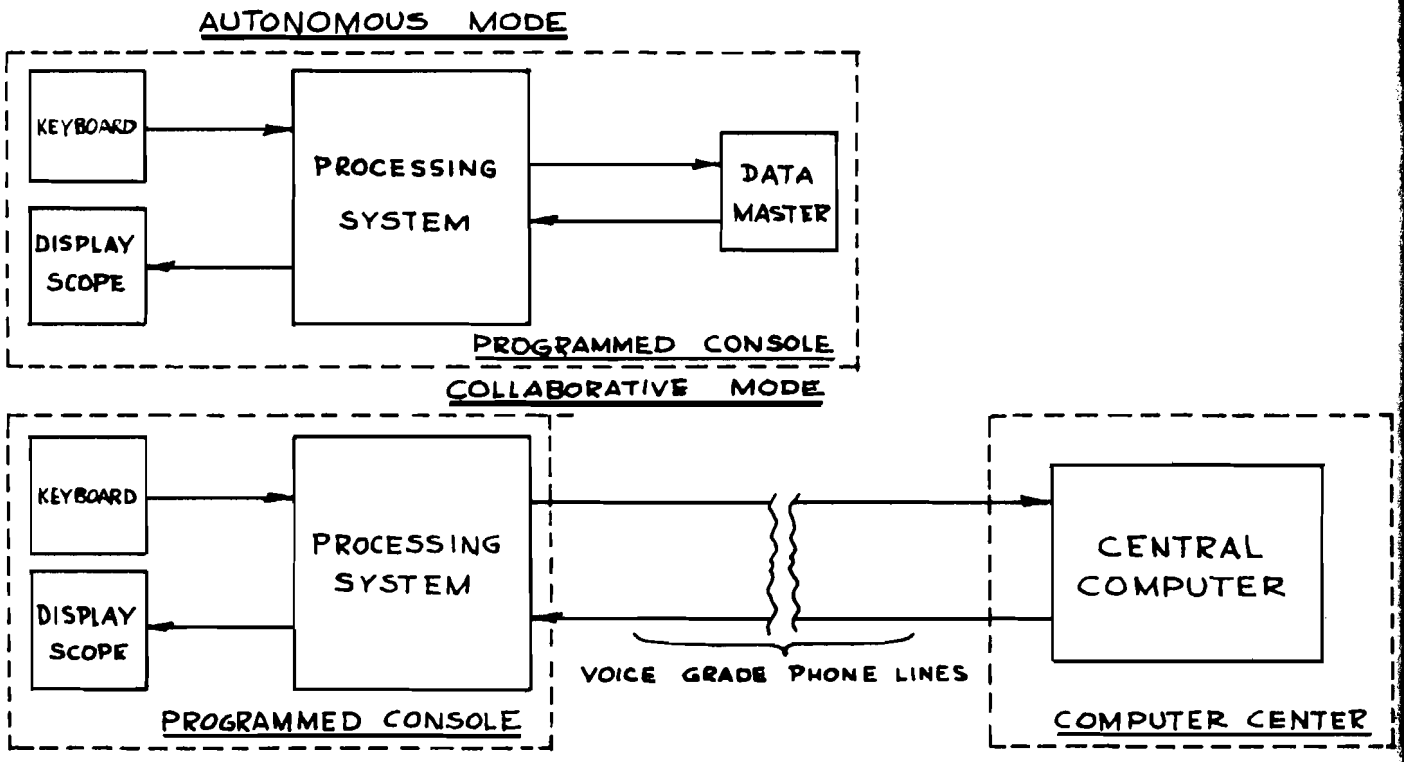

FIGURE 1. BLOCK DIAGRAM SHOWING THE AUTONOMOUS AND COLLABORATIVE MODE OF OPERATION OF THE PROGRAMMED CONSOLE.

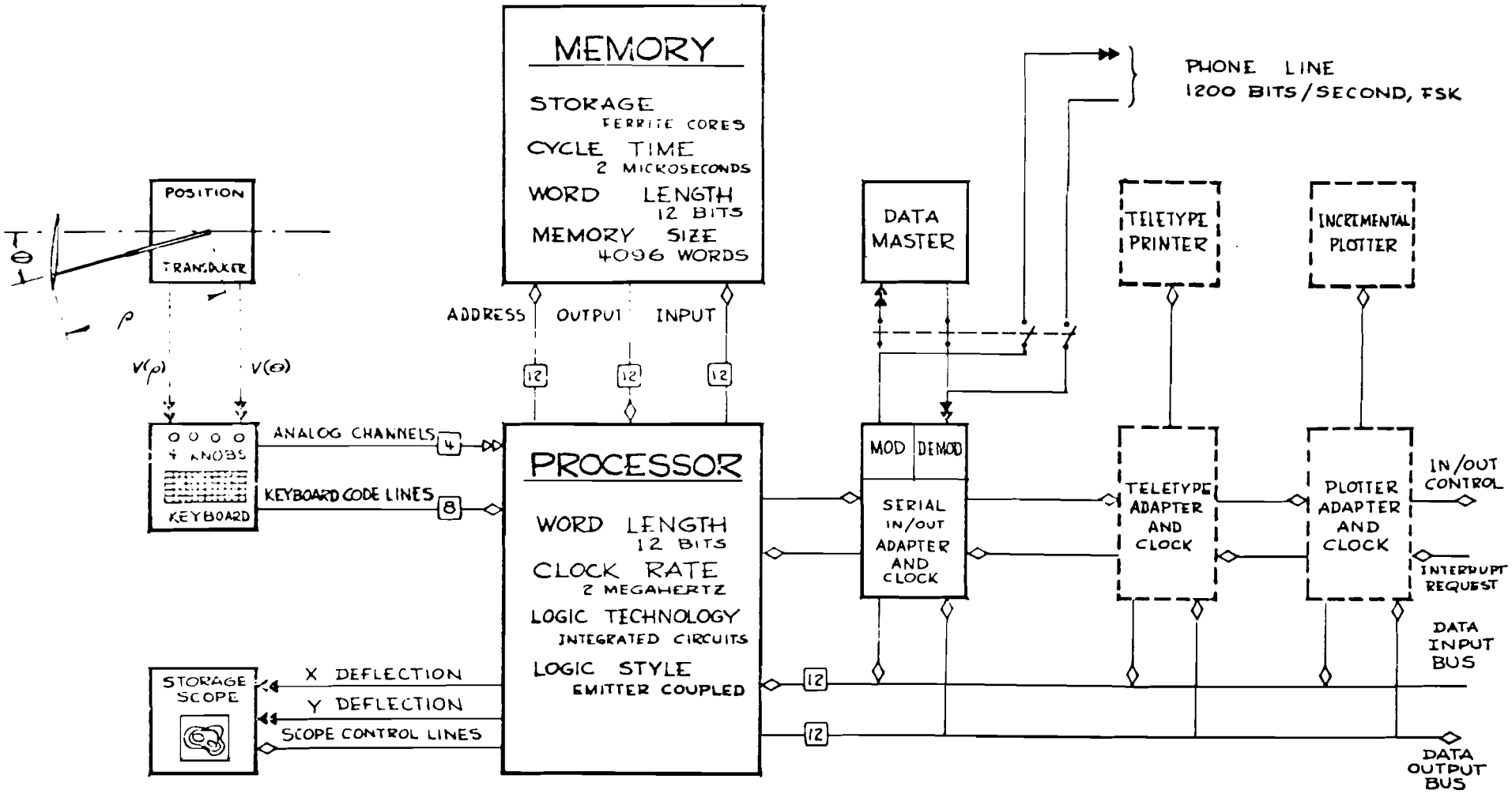

FIGURE 2. BLOCK DIAGRAM OF THE PROGRAMMED CONSOLE SHOWING STANDARD EQUIPMENT (SOLID LINES) AND OPTIONAL EQUIPMENT (DASHED LINES)

2. LINC Precision Display System

Personnel: J. R. Cox, Jr., BCL
R. E. Hitchens, BCL

Support: FR 00161

A precision display system has been constructed using the ITT model KM 105 computer display oscilloscope. Features of this unit include a display area ten inches square and a twenty mil spot size. The LINC interface was built from Flip Chip modules and is housed in a data terminal plug-in-unit. It includes intensifying circuitry and two 12-bit buffer registers and digital-to-analog converters to provide vertical and horizontal deflection voltages. To display a point, the user loads both buffer registers from the accumulator using the operate instructions. The point so selected is automatically intensified after the vertical buffer has been loaded.

This display system has proven particularly useful in conjunction with programs used to monitor ECG waveforms of patients in the cardiac intensive care unit (see A-6, C-7).

3. Cochlear Model

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

Support: FR 00161
NB 03856

Work is continuing on a mathematical model of the Guinea pig cochlea. A LINC computer program is in use which solves numerically a second-order differential equation encompassing the models of Zwislocki, Fletcher, and Peterson-Bogert. The program has made it convenient to check some of the results obtained by these investigators.

If a suitable value is chosen for the acoustic loss in the cochlear partition, the solution agrees quite well with Bekesy's observations of the Guinea pig cochlea. However, Bekesy's data exists only for low frequencies and apical positions along the cochlea.

An attempt has been made to use cochlear microphonic data to test the model at higher frequencies and more basal positions. An important test of the model is the way in which the response falls off with frequency. Unfortunately CM data from basal positions tends to be nonlinear at high frequencies for all but very low levels of stimulation. Corresponding phase data cannot be measured at these low levels of stimulation with our existing equipment.

Bekesy has observed very linear input-output functions for the displacement of the basilar membrane at the extreme levels of stimulation required for visual observation. Where we observe nonlinear CM (less than 80 db SPL), the displacement of the basilar membrane should be less than $6 \cdot 10^{-3}$ microns peak to peak (extrapolated from Bekesy's data). This makes the displacement of the membrane 10^{-4} the

width of the membrane, 10^{-4} of the shortest possible wavelength along the membrane, 10^{-6} the length of the membrane, and 10^{-2} the thickness of the basilar membrane. It seems unlikely therefore that the nonlinearities observed in the CM data are present in the mechanical motion of the basilar membrane, but are produced somewhere in the very delicate transducer mechanism which generates the cochlear microphonic voltages. Additional study will be required to determine if the CM data can be used as a quantitative check on the basilar membrane model.

4. GRAPHA (Graph Assembler)

Personnel: A. M. Engebretson, BCL
S. R. Davisson, BCL

Support: FR 00161

GRAPHA is a program which can be used to compose graphical displays and plots. By operating the analog knobs and keyboard, data can be read from tape into memory and displayed as a line graph or histogram. The aspect ratio and position of the oscilloscope display can be adjusted. Program options such as ENTER AXIS and ENTER A LABEL allow the user to add straight lines and lettering to complete the graph. The finished graph can be photographed from the oscilloscope or plotted on an incremental plotter. Other options permit the user to save the graph format table or to make changes or deletions in the graph.

5. An Incremental Plotting System for the HAVOC Computer

Personnel: A. M. Engebretson, BCL
J. H. Satterfield, M.D., Psychiatry

Support: FR 00161
MH 05806

The HAVOC is a fixed-program computer which is used primarily for computing average evoked responses. One, two or four separate averages can be accumulated during each trial of an experiment. An integral part of the HAVOC is an analog x-y plotter which is used for recording the computational results.

The HAVOC in the department of Psychiatry was modified so that a CALCOMP 565 incremental plotter could be used instead of the standard plotter. Logic was added so that once plotting is initiated, each of the results are plotted in sequence and appropriately spaced. When plotting is completed the paper automatically is advanced to a new starting position.

Publication:

J. H. Satterfield, "A System for Selection of Responses for Averaging", The Electroenceth. Clin. Neurophysiol., Vol. 21, Issue 1, pp. 86-88, June 1966.

6. ECG Rhythm Monitoring

Personnel: H. A. Fozzard, M.D., Medicine
G. C. Oliver, M.D., Medicine
F. M. Nolle, BCL
J. R. Cox, Jr., BCL

Support: FR 00161
HE 09019

In spite of considerable progress in recent years in off-line morphologic diagnosis of the ECG, methods of rhythm analysis have been less than optimal. As well, an area requiring careful rhythm analysis is intensive cardiovascular monitoring such as in coronary care units, in recovery rooms, or during surgery. If rhythm analysis is to be useful in this circumstance, it must be on-line so that maximal information is available immediately for use in care of the patients. For example, in case of an Adams-Stokes attack or a cardiac arrest, proper diagnosis and alarm is needed at least within 30 seconds. Since these events occur in an unpredictable way during phases of the patient's illness, monitoring must be continuous (24 hours a day).

The goal of this program is to provide beat by beat analysis of cardiac rhythm to identify the 30 to 40 most important rhythms. Output will provide alarms for emergency events, tabulations of useful measurements such as PR interval, QT duration, QRS width, etc., plots of VPC production rate, and English language interpretations of the rhythms. In this form it will be useful not only for coronary care units, but also for any other intensive care or recovery unit, operating rooms, or special diagnostic facilities.

Monitor programming has proceeded on the LINC computer during the past year and this work has indicated that the PC (see A-1) will be completely adequate with respect to both memory size and instruction repertoire. A sampling rate of 500 per second was chosen for the ECG signal. This is a compromise between the need to resolve the fast components of the QRS and the limitations on computing time between samples. Since at least a few seconds of waveform are needed for rhythm diagnosis, methods are being devised to reduce the needed storage space by a series of transformations on the internal signal representation. Figure 3 shows the transformation sequence. These transformations work concurrently by means of the interrupt feature. The Aztec (Amplitude Zone & Time Epoch Coding) reduces the sampled waveform to a series of horizontal and sloping line segments. This portion of the programming has been completed. A requirement of continuous monitoring is that the system identifies noise and performs analysis appropriate to the signal quality so that false alarms and misinformation can be minimized. To this end, work is proceeding on the classification of the Aztec data into one of three noise levels which determine the scope of the Primitive transformation. The Primitive transformation will then identify the QRS complexes using a generalized algorithm involving sloping line segments. For quiet data, the rest of the waveform will be categorized as arcs and grades. The Cycle transformation will identify P and T waves and determine the character of the QRS (normal, abnormal). A series of measurements are made of various instantaneous and average durations and intervals. A sequence of 5 or more cycles with their associated measurements is characterized by the Sequence transformation into specific diagnostic categories. The total memory space needed to store the data from these transformations is estimated at 1000 words.

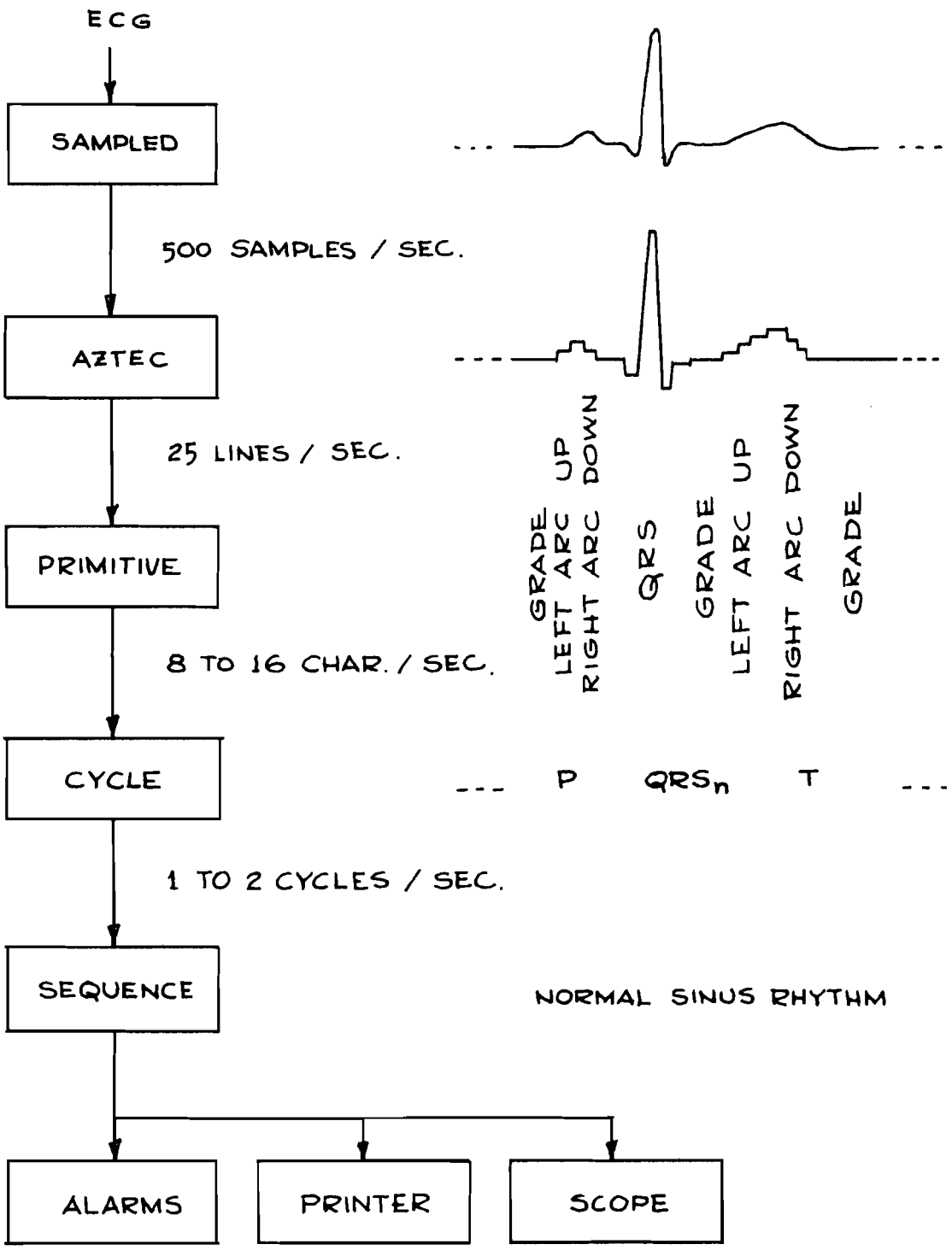

FIGURE 3. ECG TRANSFORMATION SEQUENCE

7. Detection and Enhancement of the Fetal Electrocardiogram

Personnel: D. H. Glaeser, BCL
M. R. Behrer, M.D., Pediatrics
J. R. Cox, Jr., BCL
R. B. Woolf, M.D., Obstetrics
A. I. Sherman, M.D., Obstetrics
F. L. Francis, BCL
L. Harth, B.A., Pediatrics
M. Tinnell, B.A., Pediatrics

Support: FR 00161
HE 09528
Washington University

During the past year a great deal of effort was directed toward the development and construction of an instrumentation system for data acquisition. The system was designed to provide ease of operation by medical technicians with minimal knowledge of electronic equipment. The completed system permits a single operator to control all phases of a data run including electrode placement and necessary record keeping.

The acquisition system consists of four physiologic amplifiers with controllable gain and bandwidth, a magnetic tape recorder, a strip chart recorder and a monitor oscilloscope. In addition, work is nearly complete on a coding system permitting automatic retrieval of any data (see A-8).

The attending technician need only establish amplifier gains and corresponding calibration signal amplitudes and dial a patient code into a thumbwheel switch register before initiating the pre-programmed operation sequence. All equipment is subsequently controlled by interval timers and control relays. The operation continues for 10 minutes. During this interval all data has been recorded on magnetic tape, two seven second intervals have been written on the strip chart, and calibration signals are automatically inserted on both the tape and chart records. In the future, patient codes will be automatically placed at the beginning and the end of the tape record on a channel reserved for this purpose.

Data are being investigated from a number of records selected for fetal signal quality in order to determine amplitude and duration bounds on the signal, and perhaps to establish a useful criterion for analysis which can be applied to all records. Data from 9 different records have been chosen thus far. At least three 45 sec intervals from one abdominal lead for each record have been digitized and stored on LINC tape. In addition, several short term weighted averages of the fetal signal from the same intervals have been accumulated and stored on LINC tape. The fiducial marks for these weighted averages have been obtained by a simple threshold crossing technique. A number of these averages show both P and T waves in addition to the QRS complex (see Fig. 4).

The threshold crossing technique has proven valuable in some patients on whom two simultaneous abdominal leads were recorded. Preliminary results from some of these tracings demonstrate clear FECGs in one lead but not the other, yet, using the good tracing to provide the fiducial marks, averages of the FECG are obtained from the other lead.

It is suspected that the frequent abscence of P and T waves in the averaged fetal signal may be due to inaccurate location of the QRS complex by the threshold crossing technique. Any error in locating the proper fiducial mark causes the amplitude of the average to be reduced and the duration increased. Since the P and T waves are only a small fraction of the QRS amplitude, such distortion can be very costly.

A study has been initiated, using pregnant sheep, to attempt to determine the transmission paths for the FECG from the fetal heart to the abdominal wall and the effects of intervening tissues and organs. This aspect of the project is intended to provide information concerning the mechanism of transmission. Recordings from the abdomen will be correlated with recordings taken from the uterine walls and from the fetus (es) which have been exposed by surgery. The first preparation, while providing little information about fetal signals due to inexperience with the surgical technique, served to point out several problems of surgical and recording technique.

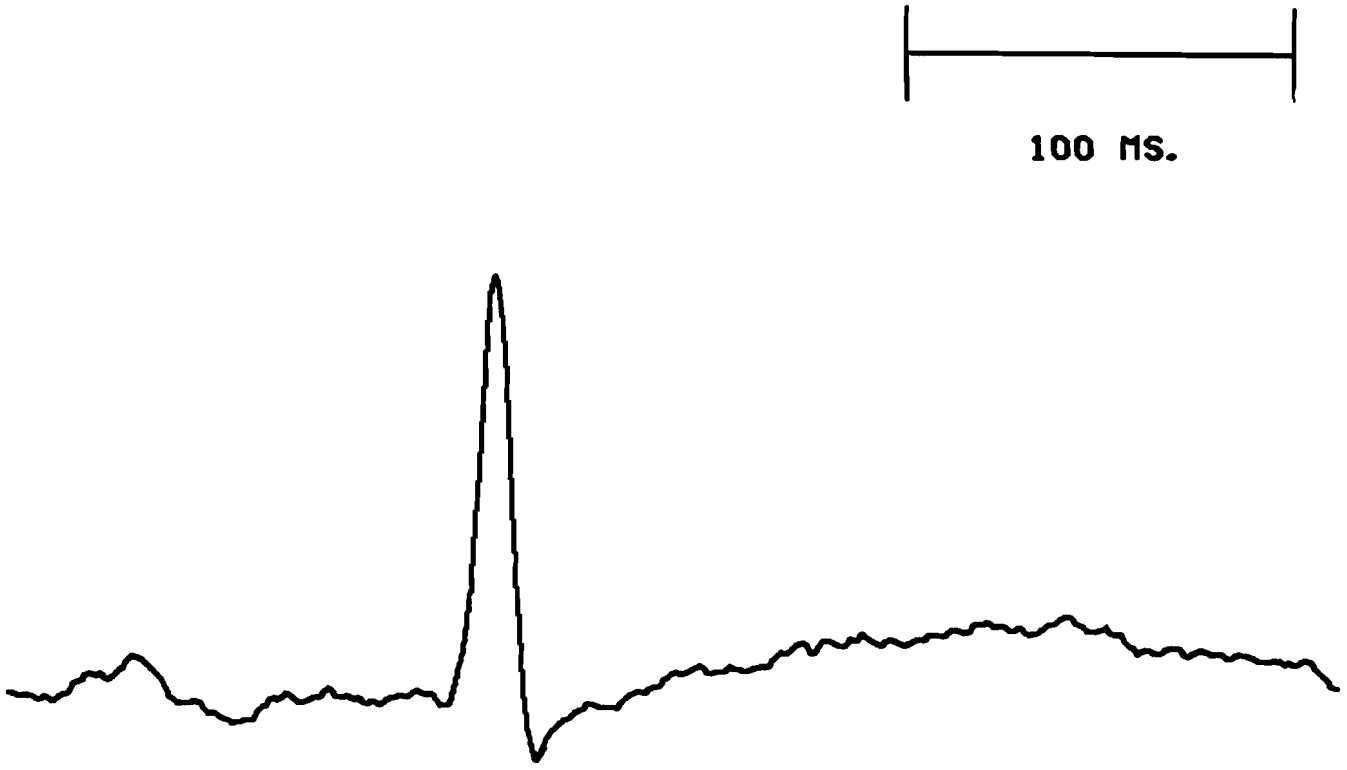

FIGURE 4. EXAMPLE OF SHORT TERM WEIGHTED AVERAGE OF THE FETAL ELECTROCARDIOGRAM.

8. Design of a Coding and Searching System for Analog Tape Recorders

Personnel: D. H. Glaeser, BCL
J. R. Cox, Jr., BCL
F. L. Francis, BCL

Support: FR 00161

For experiments in which large quantities of data are accumulated on analog tape and must be retrieved for analysis at a subsequent time, locating particular intervals of data or processing many different such intervals can be very demanding of an experimenter's time. Taped data is often ignored or discarded as it becomes older merely because of this problem. Commercial systems such as time-code generators and analog tape search equipment are very costly. The device to be described is fairly inexpensive due to its use of the LINC as an integral part of the search system.

A coder designed with DEC Flip-Chip modules to record eight decimal digits has been constructed. The format is such that the codes may be read at one capstan speed or fastwind speeds in either tape direction. Each bit is a pulse-modulated split-phase signal. Fourteen such bits constitute each of eight recorded words. The words each contain two BCD digits and associated parity bits, two bits to indicate the location of the code relative to the record (the code is written at both the beginning and the end of a record) and two bordering bits included for compatibility with a data transmission scheme used at BCL.

A data terminal plug-in-unit is used in conjunction with the LINC to provide the search feature. This data terminal plug-in-unit contains the logic required to detect the recorded pulses, determine the logical value of each bit and provide the interface with the LINC.

All portions of the system are completely tested except the equalization networks and switching required in the direct reproduce amplifier of the recorder. Total cost of modules and parts required for this equipment is about $3,000.

9. Dropout Tests of Magnetic Tape and Magnetic Tape Recorders

Personnel: D. H. Glaeser, BCL
F. L. Francis, BCL

Support: FR 00161

Evaluation of dropout characteristics of some brands of analog tape and tape recorders continued during the second year. The results of earlier tests (see BCL Progress Report No. 1) using the Precision Instruments 6100 recorder and various tapes yielded no satisfactory tape and indicated that the recorder might be a significant source of the dropout errors. Further tests were performed using an Ampex FR1300 one-half inch tape transport. Tapes from three manufacturers were tested; the procedure was identical with that of the earlier tests. Tapes tested were Memorex 62J, Ampex 748 and 3M (Scotch) 599. In a total run of 54,000 ft. of tape, no dropouts attributable to the tape were recorded. A few errors did appear in the records for all tapes, but these were much less

numerous than with the PI6100. The source of these errors may be the transport or may merely be the effects of power-line transients which have been detected frequently in the test area.

10. LINC Memory Extension

Personnel: R. E. Hitchens, BCL

Support: FR 00161

A data terminal plug-in-unit using 36 Flip-Chip cards has been built to adapt a 12-bit 4096-word core memory to the LINC. Transfers of up to 256 words between the external memory and the LINC memory are made by use of the GULP mode. Thus, a 256-word transfer requires only slightly more than two milliseconds. Provision was made for manual selection of transfers of 1, 2, 4, 8.....256 words. Alternatively, an arbitrary number of words can be specified under program control. Program set up required is the specification of starting addresses in the LINC and external memories. Thereafter, access is sequential in both memories.

11. Radiation Beam Treatment Planning Using the PC

Personnel: W. F. Holmes, BCL
J. R. Cox, Jr., BCL
H. Agress, Jr., BCL

Support: FR 00161
IBM Contract
Washington University

While treating tumors with radiation beams, the beams are often directed so as to overlap in the tumor region. This method enables the radiologist to concentrate the highest intensity of radiation within the tumor, minimizing damage to surrounding healthy tissue. In order to compute the pattern of radiation intensity within the patient, it is necessary to add the functions representing the intensity of each beam orientation and then compute a contour diagram of isodose lines. Computations for the optimal treatment plan have now become practical through the use of the PC (see A-1).

The aim of this project is to design programs for the PC that will enable the radiologist to specify any arrangement of beams and obtain an isodose countour within a few seconds. An improved method for computing isodose contours has been developed that allows for greater accuracy and more useful curves. The full programming system will: 1) allow an outline diagram of the patient to be entered using a rho-theta transducer (see A-12), 2) display on an oscilloscope the patient outline together with the position and orientation of each radiation beam (the beams will be movable), 3) calculate the intensity function for the superimposed beams, and 4) display selected isodose contours.

12. The Rho-Theta System

Personnel: G. C. Johns, Computer Research Laboratory
J. R. Cox, Jr., BCL

Support: FR 00161
FR 00218

The Rho-Theta transducer is a device for graphic input to a computer. The version of the transducer used by BCL consists of a ten-inch linear motion potentiometer (ρ) and a sine-cosine potentiometer (θ) all mounted on a gimbal arrangement. A ball-point pen is mounted at the end of the linear potentiometer wiper such that any motion of the pen on an x, y plane is reflected in the electrical output of the system. Operational amplifiers are used to resolve ρ into x and y components.

A system of LINC programs was developed for a specific type of graphic input; isodose contours used by radiologists in treatment planning. The object of the Rho-Theta programs was to store a labelled set of these contours on tape for further use as input to IBM 7072 FORTRAN programs.

Experience indicates that the analog scheme for computation of x and y from ρ and θ had serious limitations on its accuracy.

Future work will concentrate on a system that requires only voltages proportional to ρ and θ from the transducer. Resolution into x and y components will be accomplished digitally.

13. DECAL (DEsk CALculator)

Personnel: M. D. McDonald, BCL

Support: FR 00161

DECAL (DEsk CALculator) is an entirely re-written version of the program of the same name which was designed a year ago. The previous version utilized a set of double-precision floating-point subroutines, which used binary arithmetic and yielded up to seven decimal digits of accuracy. For the current version, a set of multiple-precision floating-point subroutines was written. These subroutines use decimal arithmetic and allow the user to obtain much greater precision than with the previous binary subroutines. Allowable precision is limited only by the size of the LINC memory, but the routines are currently assembled so that DECAL uses internally 30 decimal digits and the user has the option of getting either 10 or 20 decimal digits per number as output.

DECAL incorporates, besides the normal arithmetic operations of add, subtract, multiply, and divide, subroutines to take square root, natural logarithm, tangent, arctangent, hyperbolic tangent and to exponentiate. Most of the functions are evaluated using a continued fraction expansion which was found to be the only approximation which would yield the desired accuracy, up to 20 decimal digits, in anything even remotely approaching a reasonable amount of time.

14. DBLFLT (Double-precision floating-point subroutines)

Personnel: M. D. McDonald, BCL

Support: FR 00161
HE 08507

DBLFLT is a set of double-precision floating-point subroutines for the LINC originally written for use by DECAL (see A-13). Because of the possibility of their more general use, these subroutines have been separated from DECAL and are being described and distributed separately.

DBLFLT was written with two primary considerations in mind: 1) Every possible source of error was to be located and the error minimized in each instance, 2) Since the subroutines necessarily occupy a great amount of the programmable space in the LINC, the amount of space needed in the coding of the main program which uses them should be kept small by making the calling sequences short and flexible.

15. PCAP (Programmed Console Assembly Program)

Personnel: M. D. McDonald, BCL

Support: FR 00161

PCAP (Programmed Console Assembly Program) is used to assemble programs written for the PC (see A-1). PCAP operates on the LINC and is imbedded in the framework of LAP4 by means of a complete revision of the CV and CM meta commands, and modifications to LAP4 regular input and the meta commands MC, PA, and IN. Also, slight changes were made to the GUIDE convenience programs MSPRNT and MSQUIP. (A short manual on the use of PCAP was issued.)

16. PC SIM (Programmed Console SIMulator)

Personnel: M. D. McDonald, BCL

Support: FR 00161

PC SIM (Programmed Console SIMulator) is a LINC program which will interpret and execute a PC binary program (see A-1). All instructions in the PC repertoire, except LOC, REC, and IOT are properly executed.

Provisions are made so that the simulator will pause if any of certain conditions are met and exhibit to the user the current instruction, the contents of the PC accumulator, and the contents of any desired PC location.

17. LINC Teaching Programs

Personnel: P. Payne, BCL
R. M. Hesse, BCL
P. J. Kirwin, BCL

Support: FR 00161
Washington University

These seven LINC programs are designed to help the novice familiarize himself with the LINC without the need for any additional assistance. It is hoped that the programs will prove valuable as a break from reading manuals and experimentation that requires human guidance and to aid the individual in his learning process. The programs are so designed as to anticipate all possible mistakes. The areas covered by the seven programs are: 1) Introduction to binary numbers and octal notation, 2) Signed octal and binary numbers, 3) Codes for five instructions (CLR, COM, ATR, RTA, and RSW), 4) Use of these five instructions, 5) Write program to put 3710 into accumulator, 6) Write program to put 73 into relay register, 7) Write program to put 42 into accumulator, complement it, put result into relay register, clear accumulator, and put contents of relay register into accumulator.

18. Stereoscopic Presentation Utilizing the LINC Computer

Personnel: D. M. Swan, BCL

Support: FR 00161

The value of a three-dimensional presentation of various physiologic data in the biomedical sciences is obviously great. Three-dimensional vision is due chiefly to retinal parallax, i.e. the presentation of a slightly different picture to each eye. The fusion of these two images results in a perception of depth. Experience and perspective also aid in depth perception.

A preliminary program generating a separate image for each eye from three-dimensional data input has been written. The separate images are computed as if the three-dimensional data are viewed through a screen (the LINC scope). The resulting images are displayed on a one or two scope set up, the images being reduced in the single scope display. A stereoscope is used to aid in fusing the two images. Investigations concerning the use of such programs in displaying three-dimensional data such as isodose contour plots and the instantaneous electrical vector forces of a heart beat are currently under way.

V. RESEARCH PROJECTS

B. Information Processing

The following projects involve research in information processing. The work is directed toward the development and evaluation of new computational methods in support of biomedical research. Most of the work made extensive use of the facilities of the Washington University Computation Center. The listing of personnel on these projects is arranged in the same way as in Section A.

1. LINC-FORTRAN System

Personnel:
D. A. Bridger, BCL
V. W. Gerth, BCL
R. M. Hesse, BCL
G. C. Johns, Computer Research Laboratory
L. H. Snow, Computation Center
G. S. Whitlow, Jr., BCL

Support:
FR 00215
FR 00161
G 22296
FR 00218
Washington University

This system involves the use of three computers and data phone lines. The LINC is connected to the Programmed Console prototype Buffer (PCB) via data phone lines. The PCB is connected by a tape channel to the IBM 7072 located at the computation center.

A system of LINC programs was designed for the preparation of FORTRAN source programs, their filing and manipulation on LINC tape, their display on the oscilloscope and hard copy via an on-line teletype. The FORTRAN source programs can be sent to the PCB. Information received from the PCB can be stored on LINC tape to be typed out later at the operator's convenience. An elementary scan is used during the typing of the source statements to identify simple errors. Error messages are printed on the teletype.

The program written for the PCB allows it to act as a buffer between the LINC and the IBM 7072. Messages and information are routed through the PCB to their destination. Re-coding of the information also takes place so that it is compatible with the computer that is receiving the information.

The IBM 7072 program allows input from the PCB. The input is then processed as a normal batch and output sent back to the PCB or saved to be sent later.

2. Serum Electrophoretic Patterns in Normal and Abnormal Pregnancies

Personnel: R. Burstein, M.D., OB/GYN
S. C. Stevens, Ph.D., Biochemistry
G. S. Whitlow, Jr., BCL

Support: FR 00215
G 22296
Washington University

In recent investigations, the existence of a rejection phenomenon in the decidua or maternal side of the placenta was noted. This pathologic finding shows its highest incidence at about the 8th to 10th week with a marked decline after the 12th week. The above findings lend evidence to the thesis that pregnancy is in reality a transplant with the mother acting as a host. From these findings, it is noted that some change must take place at the end of the first trimester which prevents the rejection phenomena from going to completion. Previous papers on this subject have been deficient in the numbers of specimens from the first trimester which is the most significant one. To date more than 3500 specimens have been accumulated including serial evaluation on about 200 pregnant women. This would represent the largest series yet published.

The determinations of the albumin and globulin fractions of the specimens are being subjected to statistical analysis at weekly or bi-weekly intervals, (see also C-2).

3. Macromodular Processor Design Experiments

Personnel: R. A. Dammkoehler, BCL
W. E. Ball, BCL/Computer Research Laboratory
A. R. Rawizza, Computation Center
R. L. Walton, Computation Center

Support: FR 00215
FR 00218
SD 302

A series of experiments designed to evaluate the utility and effectiveness of macromodularized processing functions has been initiated during this continuation period. These investigations are being carried out over a representative range of information processing applications, from pure numerical computation to formal symbol manipulation, (e.g., natural language text editing and syntax analysis). To date macromodular designs have been completed for several machines including an algorithmic processor of the VALGOL type and a compiler-compiler based on Schorre's "META-II-A Syntax Directed Compiler Writing Language". Variations in logical organizations of these machines are now being developed in preparation for simulation studies utilizing the 360/50 version of the macromodular systems simulator. In addition, a prototype design for a general purpose parallel processor and a preliminary version of a highly specialized text editing processor are in early stages of development.

4. A Macromodular Systems Simulator (MS2)

Personnel: R. A. Dammkoehler, BCL
R. A. Cook, Computer Research Laboratory
R. I. Berns, Computation Center
D. A. Bridger, BCL

Support: FR 00215
FR 00218
SD 302

The macromodular systems simulator is a control program and programming language implemented at Washington University to facilitate the design and subsequent realization of macromodular computer systems. The macromodular concept, developed by Clark, differs significantly from earlier machine design approaches in that it permits the definition of any information processor in terms of a small number of basic elements called macromodules. Furthermore, a method for the control of these macromodules, discovered by Stucki and Ornstein, minimizes the usual timing constraints, and greatly simplifies the computer design process. However, a potentially more important consequence of their control scheme is that a macromodular control network for a given process is isomorphic to the flow diagram describing that process. Thus, systems organization is implied by the programmer's flow chart in essentially the same fashion as it implies the structure of a machine language program. It can be shown that program subroutines may be replaced directly by macromodular sub-systems and vice versa. In fact, it is relatively easy to show how the macromodules can be used to build copies of existing computers, and/or to implement complex processing programs in hardware form.

The MS2 control program and language enable an engineer or programmer to design macromodular systems and run programs on such systems simulated on a convential digital computer. Input to the simulator consists of a standard set of function definitions for the basic macromodules, a description of the organization of the target machine, the program to be executed by the target machine, and data required by that program. Output from the present version of MS2 is an active level change map (a continous trace of the internal control network of the target machine as it executes its program) and the results of computations performed by the target machine. A procedure for preparing wiring tables and diagrams has been developed and will be incorporated into an improved version of the simulator.

The simulator is implemented in TRAC, a string processing language, selected because of the similarity between the macromodular control network and Mooers' concept of an active string. By using a combination of TRAC primatives, it is possible to exactly duplicate the functional characteristics of most of the present set of macromodules. The exceptions are the control branch, a macromodule used to initiate parallel control networks, and the interlock module which functions as a priority selector at the intersection of multiple control paths. As parallel operations must be simulated sequentially on a serial machine, the functions of these two modules are handled internally by the simulator control program. However, in order to preserve the validity of the level change map and wiring tables, both control branch and interlock macromodules can be included in the description of the target machine.

Most, if not all, of the limitations of the operational version of MS2 arise from the fact that it is implemented on a fixed word length (10 digits and sign) decimal machine (IBM 7072), while the basic macromodular registers, adders, and memory units are 12-bit binary devices. The obvious compromise was made such that arithmetic and logical operations are defined for 4-place octal numbers and information stored in the memory of the target machine is normally a string of four octal digits. Used as an address, these digits correspond to 4096, the maximum size of a basic macromodular memory unit. Because the simulator and the target machine must simultaneously occupy the same memory, it is impractical to run simulated programs requiring more than 4096 word storage capacity. In order to avoid the constraints imposed by the 7072, an expanded version of MS2 is being written for an IBM 360/50.

5. Symbolic Information Processing

Personnel:
R. A. Dammkoehler, BCL
W. E. Ball, Computer Research Laboratory
W. W. Wayne, Computation Center
R. I. Berns, Computation Center
D. E. Burlingame, Computation Center
A. M. Olson, Computation Center

Support:
FR 00215
ES 00139
FR 00161

Research initiated by W. E. Ball has demonstrated the feasibility of a computer-based processing system which facilitates the formulation and evaluation of mathematical models of complex biological phenomena. In a continuing effort to utilize the power of the digital computer to the advantage of the biomedical investigator, a program (AUTOMAST) has been developed which accepts as input a system of ordinary differential equations and generates both symbolic and numeric solutions. A second program for statistical analyses, (STAT) which accepts as input both numeric data and symbolic equations describing linear systems, has been completed and tested. The algebraic manipulation routines utilized by AUTOMAST are presently being combined in the creation of AUTOSTAT, a system designed to be used with the Programmed Console (PC) in a collaborative mode (see A-1). A third program (AUTOMODL) which derives synthetic models of multivariate, nonlinear time dependent phenomena, will make possible the generation of the n^{th} order system of differential equations providing the best fit to experimentally obtained input and response measures. By using AUTOMAST, AUTOSTAT and AUTOMODL, an investigator may develop and evaluate rather sophisticated mathematical models without writing any computer programs or doing any laborious algebraic manipulation, or conveniently postulate and analyze alternative nonlinear models of biological phenomena while avoiding the difficult and time-consuming task of deriving and simplifying the alternative sets of nonlinear normal equations.

Publication:

W. E. Ball, R. I. Berns, "Automast--Automatic Mathematic Analysis and Symbolic Translation". Presented at the ACM Symposium on Symbolic and Algebraic Manipulation, Washington, D.C., March 29-31, 1966. To be published in the August 1966 issue of the COMM. of ACM.

6. Information Storage and Retrieval

Personnel: R. A. Dammkoehler, BCL
M. Bhide, BCL
J. P. Miller, BCL

Support: FR 00215
G 22296

A series of experiments, designed to evaluate the appliciability and effectiveness of various computer-based techniques for automatic classification and retrieval of biomedical literature, was completed during 1965-66. A collection of 438 author-written abstracts, each less than three hundred words, dealing with the diagnosis and treatment of cerebrovascular disorders, lipid metabolism, rheology, viscometry and neurosurgery was used as the experimental document corpus. This file was key-punched in free form, converted by machine to standard KWIC format and a complete concordance generated utilizing two specialized programs written by M. Bhide. By-product data from this preliminary analysis included word lists, frequency indices, and document-term occurrence tables.

Three alternative methods of automatic descriptor identification were employed; one based on frequency (Borko and Bernick), a second based on the distribution parameters of 450 nominatives (Eldridge and Dennis) and a third based on factor analysis of the simple occurrence of the 100 most frequently appearing nominatives. The resulting lists (L1, L2, L3) of descriptors were used for classification experiments; however, as the frequency list and the distribution parameter list were identical for this small sample, the latter was excluded from any further consideration.

Preliminary analysis of the results obtained thus far suggests the following interpretation:

(a) Frequency dependent techniques cannot be used effectively for classification and/or retrieval of the literature related to cerebrovascular diseases. This may in part be due to the precision of the language used by the physician and biomedical researcher, (e.g. high content bearing terms do not appear frequently).

(b) For a small sample of documents distribution parameter methods produce the same unreliable results as frequency dependent techniques.

(c) Classification methods based on co-variance or co-occurrence data are inadequate and insensitive to the effects of higher order term-term interaction. However there is a distinct possibility that multi-term concept descriptors may be derived from factor analyses of simple occurrence data. Although the associated factor weights have no numerical interpretation, highly weighted terms can then be used as attributes of the document corpus.

(d) In limited experiments, conducted to date, the linear associative retrieval technique (Jones and Guiliano), which capitalizes on higher order

term-term association appears to produce valid classification and retrieval responses. CAUTION: A great deal of additional work will be necessary to confirm this hypothesis.

(e) Examination of those cases in which the linear associative retrieval scheme fails, indicates that this technique is insensitive to syntatical differences in term usage.

7. A Computational Procedure for Parameter Estimation Applicable to Certain Nonlinear Models of Enzyme Kinetics

Personnel: R. A. Dammkoehler, BCL
J. W. Josse, M.D., Microbiology and Physiology

Support: FR 00215
GM 10642

Parameter estimation and evaluation of alternative linear models of biophysical phenomena may be readily accomplished through the application of conventional methods of statistical analysis. However, when the theoretical models are nonlinear and the parameters are not independent functions of the dependent variable, the analysis is neither straightforward nor easily performed without computational aids. Three major problems are commonly encountered. First, the nonlinearity of such models, especially when compounded by the effects of experimental error in the measured variables, makes parameter estimation a difficult computational problem. Second, and most important, the interdependence of the parameters precludes the use of standard statistical procedures. Third, there is no method other than exhaustive search which will guarantee that the numerical estimates are optimal (i.e. that the derived parameter values are the "best" least squares estimates).

Current research in applied mathematics and statistics has produced several techniques which appear to be generally useful for the solution of such problems. A new algorithm for least squares estimation of nonlinear parameters developed by Marquardt has proven to be an efficient method for computing values of the interdependent parameters. Similarly, a method advanced by Quenouille provides a mechanism for estimating the standard error of the parameters, even though the distribution of the general population is unknown. When implemented on a digital computer and used in accordance with the strategy described in the publication noted below, these techniques provide an effective tool for the analysis of nonlinear models. Although the problem of distinguishing the global optimum from secondary local optima is not resolved, this strategy provides ample opportunity for minimizing the probability of such errors. Since complete analysis requires the computation of n + 1 sets of parameter estimates, a wide range of potentially optimal solutions may be examined by choosing different starting values for each evaluation. For each set of parameter estimates, the statistic ϕ, a measure of goodness of fit,

$$\phi_j = \sum_{i=1}^{n-1} (v_i - \hat{v}_{ij})^2 \qquad j = 1,2,\ldots n$$

is computed where

$$\hat{v}_{ij} = f\ (x_1, x_2, \ldots x_n, b_{ij}, \ldots b_{kj}).$$

The ϕ_j values may be compared with the value obtained over all n observations, $\phi_{(n)}$. Experience has shown that one or more of these intermediate solutions may yield ϕ_j values which are significantly smaller than $\phi_{(n)}$. By using the numerical parameter estimates associated with the smaller ϕ_j as starting values for another complete analysis, an improvement in $\phi_{(n)}$ can be obtained. The statistic $\phi_{(n)}$ is a variance measure and may be easily converted to a standard error estimate S_e by dividing by $(n - k - 1)$, where k is the number of parameters of the model. The decision rules for determining a significant difference between $\phi_{(n)}$ and any ϕ_j may be expressed as an F ratio test, with the null hypothesis expressed as $\phi_{(n)} < \phi_j$ or, more conventionally, as $S^2_{e(n)} < S^2_{e(j)}$, where

$$F = \frac{S^2_{e(n)}}{S^2_{e(j)}}$$

The degrees of freedom associated with $S^2_{e(n)}$ and $S^2_{e(j)}$ are $(n - k - 1)$ and $(n - k - 2)$, respectively. Thus, for any predetermined confidence level, e.g. $\alpha = 0.05$, the critical value of F is constant for each analysis and can be used to automate the analysis strategy fully. This decision process has been included as an integral part of the computer program used in this research.

Publication:

R. A. Dammkoehler, "A Computational Procedure for Parameter Estimation Applicable to Certain Nonlinear Models of Enzyme Kinetics", The Journal of Biological Chemistry, 241, No. 9, pp. 1948-1957, May, 1966.

8. Numerical Taxonomy

Personnel:
R. A. Dammkoehler, BCL
J. H. Satterfield, M.D., Psychiatry
M. Bhide, BCL
K. E. Shumate, BCL
J. M. Vanderplas, BCL

Support:
FR 00215
FR 00161

The use and evaluation of numerical techniques for the classification of patients on the basis of common symptoms and clinical observation was continued. Three specific problems encountered in earlier experiments were considered in detail: a) identification of prime nodes and initial case constellations, b) development of precise methods of clustering, and c) automatic reduction of attribute space.

A number of approaches to these problems were postulated and tested in a series of limited experiments. Included were a heuristic method of discrimination using a combination of multiple regression and Boolean category analysis, a procedure for redimensioning the elements in a Boolean lattice by iteratively weighting selected attributes, and clustering criteria based on a linear combination of entropy and distance measures. Although substantial agreement between the derived patient clusters and clinical diagnosis was observed in some experiments, there is as yet no indication that such methods produce consistent and reliable classifications.

9. Optimization of Radioactive Dose Rate Distributions for External Beam Sources

Personnel: T. L. Gallagher, BCL
W. E. Powers, M.D., Radiology

Support: FR 00215
Washington University

A program of research has been initiated which considers the maximization of integral dose rate in a specified tumor region subject to a constraining set of minimizing conditions in non-tumor regions. These conditions may be point constraints or region constraints. The method of solution consists of a sequential combination of linear programming, pattern search, and heueristic techniques to determine the optimum values of the following variables:

1) Number of beams.
2) Strength of beams.
3) Port size.
4) Angle of beam incidence.

Presently all beams are directed to a common central point, which is assumed to be the center of the tumor, and the beams are moved in an arc of radius R about this point. Each beam may be moved at any particular radius independent of the other beams.

Mathematically the problem may be formulated as

$$\text{Maximize:} \quad \sum_k \left(\sum_i \sum_j d_{ij} \right) S_k, \text{ with } i,j \in A;\ k=1,2,\cdots K \qquad (1)$$

$$\text{Subject to:} \quad \sum_k \left(\sum_i \sum_j d_{ij} \right) S_k \leq N_1, \ i,j \in C_1$$

$$\vdots$$

$$\sum_k \left(\sum_i \sum_j d_{ij} \right) S_k \leq N_m, \ i,j \in C_m \qquad (2)$$

$$\vdots$$

$$\sum_k \left(\sum_i \sum_j d_{ij} \right) S_k \leq N_M, \ i,j \in C_M$$

$$k=1,2,\cdots K$$

where i, j are spatial indices which take on all specified values within a particular region; m is the constraint index with maximum value M; k is the beam index with maximum value K; d_{ij} is the attenuation kernel for the (i,j)th spatial point and contains implicitly the effects of port size and angle of beam incidence; A is the region of maximization; C_m is the mth constraint region; N_m is the dosage bound for the mth constraint region; and S_k is the source strength for the kth beam.

The procedure of variable evaluation proceeds as follows:

1) The S_k are evaluated which maximize equation (1). (Some of the S_k may be eliminated.)

2) Using only the S_k which maximize, a pattern search is made by pertrubing the angles of beam incidence to determine the direction of movement of the beams.

3) Port size adjustment can then be made heueristically depending on the uniformity of the dose rates in the region of maximization or on field balancing. (This step has not been fully implemented.)

4) Return to step 1) for continued iteration unless no further improvement can be made in the maximum value of equation (1).

Even though this method is still under development it seems that this procedure may open a fruitful pathway to external beam optimization.

Publication:

T. L. Gallagher, W. E. Powers, "Optimization of Radioactive Dose Rate Distributions for External Beam Sources", Presented at the International Conference on the Use of Computers in Therapeutic Radiology, Cambridge, England, 14-17 June 1966. To be published.

10. Implant Dosimetry Using the Programmed Console

Personnel: T. L. Gallagher, BCL
Wm. E. Powers, M.D., Radiology
S. J. Smith, Computation Center

Support: FR 00215
FR 00161
G 22296
Washington University

Through the use of a small computer known as the Programmed Console (see PC description in A-1), the job of translating from therapists' language to computers' language will become greatly simplified. The PC, by suitable programs, will allow the therapist to interact directly and easily with a complicated, accurate, and useful computer program which runs in a large-scale computer possibly located remotely from the hospital.

The program computes the dose-rate distribution through the direct evaluation of the Sievert integral by 3-point Gaussian quadrature. Dosage values are calculated for each of five planes with a grid of 21 by 21 points.

A program is being written for the PC which allows the therapist to conveniently complete the necessary input information for an implant calculation through the use of multiple-choice and simple fill-in-the-blank questions. Checking of some critical input values will be performed by the Programmed Console, and a complete review of all input parameters may be made through visual inspection by the therapist of a series of textual scope displays.

Interrogation and option-choice routines which utilize the output information from the central machine calculations are being written. The routines will allow the investigator to display standard isodose curves, plane by plane; to add or delete isodose curves from these planes; and to change the scale within the plane.

Remote operation with the Programmed Console should bring the investigator significantly closer to a large-scale computer than has heretofore been possible.

Publication:

T. L. Gallagher, Wm. E. Powers, S. J. Smith, "Implant Dosimetry Using the Programmed Console", Presented at the International Conference on the Use of Computers in Therapeutic Radiology, Cambridge, England, 14-17 June 1966. To be published.

11. Geometric Factor Analysis

Personnel: R. L. Hamblin, Ph.D., Computation Center
R. A. Dammkoehler, BCL

Support: FR 00215

In psychophysics during the past 12 years, S. S. Stevens has developed a number of measurement procedures which yield ratio scales. However, these are not equal ratio scales which are ordinarily obtained in the physical sciences, but unequal scales. Often different types of ratio measurement (x_i and x_{ii}) of the same variable (x) are related not linearly but curvilinearly as a power function of the form:

$$x_i = C\, x_{ii}^{n}$$

where the exponent n is ordinarily not equal to 1.0. Preliminary indications suggested that many, if not most, measurements of behavior when at the ratio level, are of the unequal variety. Traditional factor analysis assumes linear relationships and it assumes normal distributions or measurement error rather than log normal distributions which apparently characterize these data. To adapt traditional factor analytic procedure for use with this kind of data, certain straightforward modifications were made, producing a new Geometric Factor Analysis technique. First, the raw unequal ratio measurements are transformed to logarithms. This makes the relationships linear ($\log x_i = \log C + n \log x_{ii}$), and it normalizes the lognormal error distributions. Secondly, the correlations are calculated using the log transformed data, the factors extracted and rotated to simple structure as usual.

Thirdly, a weighted geometric mean is used to calculate the index (I) of the underlying variable, x, using n measures as follows:

$$\log I = \frac{1}{n}(w_1 \log x_1 + w_2 \log x_2 + \cdots + w_n \log x_n)$$

Preliminary tests suggest that this procedure yields especially tight factors with behavioral data. The correlations with the underlying variable, the w's are often in the high .90's, and the index appears to improve the reliability of the findings. The appropriate production programs for geometric factor analysis are in the process of being completed.

12. Biomedical Data Processing Research

Personnel: J. M. Vanderplas, BCL
J. P. Miller, BCL
D. A. Bridger, BCL

Support: FR 00215
G 22296

Two computer programs, one to compute Bayesian posterior probabilities and one to compute prime implicants of disjunctive Boolean functions, were tested, modified and used for experiments during the period of this report.

Two major experiments were undertaken, employing data gathered by the St. Louis County Health Department. The first experiment consisted of a Bayesian posterior probability analysis on a sample of 846 subjects on whom 22 variables, representing symptoms and mental health status, had been measured. The dependent variable chosen was the level of clinical disturbance, rated on a five-point scale. Twenty-one independent variables, representing symptoms, such as temper tantrums, eating and sleeping disturbances, night terrors, and similar disturbances, were also rated on a five-point scale. The experiment was conducted to determine if the posterior probability of clinical disturbance could be related differentially to the various configurations of symptoms. The results confirmed an intuitive expectation that such a large number of variables taken on a sample of this size could result in a number of symptom configurations equal to the sample size. That is, the number of combinations of the 21 variables, rated in this way, had configurations such that the probabilities for any given symptom configuration would result in equiprobable--and thus undifferentiable--levels of clinical disturbance. In order to reduce the number of possible configurations, the data were recoded by splitting at the median value and coding them 0 or 1 if they were below or above the median, respectively. Although this recoding tended to reduce the number of configurations, the result of a second analysis indicated that there would still be a sufficient number of unique configurations to make discrimination of the levels of clinical disturbance difficult, if not impossible.

In order to reduce the data further and to see if the configurational structure could be simplified, the data were subjected to Boolean reduction using the method of Quine. Duplicate configurations were removed from a sample of 437 cases all having the same level of clinical disturbance. This left 296 unique configurations unduplicated. The Boolean reduction program resulted in 270 prime implicants and 26 unique minterms. These data are currently being

examined both for the purpose of determining a minimum taxonomic structure and for reanalysis using the Bayesian program. It is hoped that a combination of Boolean reduction and Bayesian probability analysis will provide a method for obtaining maximum discrimination among the levels of clinical disturbance based on the symptom configurations.

A second experiment was conducted along the lines similar to those above on a sample of 111 cases with one dependent variable (mental health status) and six symptom variables. The results were fairly dramatic, probably due to the nature of the data. The data originally were in the form of rating scales (0-5) with symptoms including general appearance, self-esteem, interpersonal relations, etc., and general mental health status. When the data were recoded (0-1) and subjected to Bayesian analysis, it was found that the disturbed group (those having low general mental health status) was distributed across seventeen unique and mutually exclusive symptom configurations, while the undisturbed group (high mental health status) was distributed among the eight symptom configurations only seven of which were identical to those across which the disturbed group was distributed. When these data were analyzed, the posterior probabilities permitted discrimination between the two groups with 91% reliability on the sample examined. These data are currently being examined further using a Boolean reduction analysis in the hope that the symptom configurations can be further reduced and simplified.

The data of the second experiment were also examined from another point of view in order to provide a comparison between a more traditional means of analyzing them (multiple regression) with the Boole-Bayes approach. The sample of 111 cases was subjected to a multiple regression analysis, the results indicating that the overall mental health status could be predicted from the symptom configurations with a multiple correlation of .812. The partial correlations between the independent variables (symptoms) and general mental health status were distributed in such a fashion as to indicate that three of the symptoms contributed most heavily to the multiple correlation. The data for these three symptoms were again recoded and subjected to Bayesian analysis, as above. The posterior probabilities permitted discrimination between the groups with 90% reliability -- as compared with 91% using all six symptoms. Thus, using the multiple regression technique to determine which symptoms are important in predicting general mental health status, and then subjecting the symptoms to the Boole-Bayes analysis provides a heuristic technique for determining discrimination capability of such data.

Although the multiple regression technique could be used by itself, the difficulties involved in interpreting the results based on the presence or absence of nominal symptoms, represented as continous variables, are circumvented by the further use of Boolean reduction and a Bayesian probability analysis. The multiple regression approach thus serves as a means of identifying significant partial variables, with the final analysis being conducted using the Boole-Bayes' approach.

V. RESEARCH PROJECTS

C. Collaborations with Other Organizations

The following research projects have been carried on for the most part in other laboratories, departments, or institutions. Responsibility for the research lies outside the Biomedical Computer Laboratory. However, portions of these projects involve collaboration with, or supervision by staff members of our laboratory. In some cases the research has been supported by funds from our laboratory. To make clear the goal of the research the complete project is outlined. Special mention of the collaborative efforts is made where they deal with only a portion of the project.

1. Averaging Techniques for Extracting Acoustic Signals from Noise

Personnel: M. K. Bauer, B.S., Central Institute for the Deaf
A. F. Niemoeller, Sc.D., Central Institute for the Deaf
J. R. Cox, Jr., BCL

Institution: Central Institute for the Deaf

Support: NB 03856
FR 00161

A SIGnal AVGeraging program was written for the LINC computer to extract repetitive signals from noise. The frequency range covered by the SIGAVG program is from 20 cps with a resolution of 512 points per period to 30 kc with 16 points per period. Two sampling procedures are used to cover this frequency range, both of which use a specially designed data-terminal plug-in-unit. This module contains an external clock capable of being started and synchronized with an external signal. For frequencies between 20 cps and 700 cps, the waveform is sampled and averaged continuously. The plug-in-unit synchronizes the computer and thereby eliminates starting time jitter. For signals above 700 cps a technique, similar to that used in sampling oscilloscopes, is used along with the external clock to achieve an effective sampling rate of 500,000 samples per second. The running sum of the stored samples is displayed on the LINC scope. Upon completion of sampling, the results can be scaled, vertical amplitudes read with a movable cursor, and the waveform can be smoothed to remove scattering of points. The results can then be labeled for future reference and stored on tape.

A survey of a number of special-purpose commercial signal averaging devices was made. Important operating and convenience features found on these units were incorporated into the SIGAVG program or are already available in the LINC hardware.

2. Data Gathering Techniques for Electrophoretic Patterns

Personnel: R. Burstein, M.D., OB/GYN
H. R. Grodsky, BCL
H. Agress, Jr., BCL
J. R. Cox, Jr., BCL
R. M. Hesse, BCL
R. G. Loeffel, BCL

Institution: Jewish Hospital

Support: FR 00161
FR 00215
Washington University

This work with electrophoretic patterns on cellulose acetate uses a Beckman Model RB Analytrol to plot a curve of the density of the serum sample versus distance. The curve is continuous and appears as five or six humps; four globulins, albumin and sometimes an unknown quantity "X".

Because of the large number of patterns involved in this study, an interface and programs have been completed to allow the LINC to obtain the normalized areas directly from the Analytrol. The curve is plotted by a pen which is driven by a servo motor. Since no voltage proportional to the pen deflection is available within the device, a single-turn precision potentiometer has been connected to the servo motor. The voltage derived from the potentiometer is sampled by the LINC and a program has been written which locates the five or six humps and performs the necessary integration. These values are then stored on tape to be used in future statistical analysis, (see B-2).

3. EXP 3 (A Program for Fitting Exponential Decay Curves)

Personnel: I. A. Coret, M.D., Pharmacology, St. Louis University
M. D. McDonald, BCL

Institution: St. Louis University

Support: FR 00161
HE 08507
St. Louis University

A LINC program was written to facilitate the fitting of a curve of the form $y=ae^{-\alpha t} + be^{-\beta t} + ce^{-\gamma t}$ to data gathered from experiments designed to show the change of length of a certain type of smooth muscle after abrupt immersion in various chemical agents of physiological importance e.g., epinephrine, acetylcholine, and histamine.

The empirical curve may be entered into the system, as may ranges for the six parameters a, b, c, α, β, γ; these input values may be saved and restored to the system as desired. The values of the parameters within the specified ranges are controlled by the settings of six of the LINC potentiometers. The knobs are continuously sampled and a function of the above form evaluated and displayed on the scope along with the empirical curve. The current value of the parameters may be printed out at any time. This program has been used primarily as a first step, a way to obtain an initial approximation which was later refined by an iterative procedure on the IBM 1620 at the Yalem Computer Center of St. Louis University.

4. Transmission of Data from a Microspectrophotometer

Personnel: J. M. Enoch, Ph.D., Ophthalmology
J. R. Cox, Jr., BCL
R. E. Hitchens, BCL

Department: Ophthalmology

Support: NB 02168
FR 00161

A system design has been completed for instrumentation to be used in an experiment directed at measuring the effect of monochromatic light of varying wavelength on retinal tissue. The design is centered around a 12-bit parallel-to-serial converter. The converter, used in conjunction with a commerical data set, will transmit information via telephone lines from the Department of Ophthalmology to a LINC at BCL. Input to the converter is from toggle switches, a 10-bit shaft encoder, and a 10-bit analog-to-digital converter.

5. Control and Analysis of Current-Voltage-Tension Relations in Muscle

Personnel: H. A. Fozzard, M.D., Medicine
D. C. Hellam, M.D., Medicine
J. R. Cox, Jr., BCL

Department: Medicine

Support: FR 00161
HE 09019

While the Hodgkin-Huxley voltage clamp analysis has been highly successful for nerve fibers, characterization of the ionic basis of muscle membrane electrical events has been much less satisfactory. As well, little direct evidence has been available in the voltage and/or current characteristics of excitation-contraction coupling in muscle. There has been promise recently that small pieces of cardiac cell membrane can be clamped by using an intracellular electrode for current passage, but this is limited by the ability of electrodes to carry adequate peak currents and total charge. Use of the LINC is planned to control the sequence of measurements in an optimal fashion so as to avoid overloading the electrodes and to provide rapid analysis of the data for immediate use in the experiment. At present a method of data modification has been developed (AZTEC - see A-6), and the control and analysis systems have been reduced to flow diagrams. The programs will be used first to analyze taped data from several membrane equivalent circuits, and later in the experiment itself. Advice on program development was provided by BCL.

6. Thoracic Impedance Waveforms Related to the Cardiac Cycle

Personnel: H. A. Fozzard, M.D., Medicine
S. P. Londe, M.D., Surgery
F. M. Nolle, BCL
M. E. Dodge, B.S., Medical Student

Department: Surgery

Support: FR 00161
Washington University

At present no satisfactory device is available for continuously monitoring cardiac function non-surgically other than the ECG. Such a device would be an important component of any cardiac monitoring system.

Preliminary investigation has begun into the use of thoracic electrical impedance as a parameter of cardiac function, specifically its use in measuring cardiac output. An on-line program has been written for the LINC computer to sample the ECG at 2 msec intervals and the 50 kc thoracic impedance at 10 msec intervals. The impedance signal is passed through a digital band-pass filter with cutoff frequencies of 0.7-5.0 cps to reduce noise levels and respiratory baseline drift. A weighted average of thoracic impedance is formed over a 1.28 sec time interval whose initial point is 310 msec prior to the R-wave peak. Initial examination of the waveform in the human and the anesthetized dog show it to be complex and composed of several components. Variability with electrode placement was also noted in the human subject.

7. Establishment of a Coronary Care Unit

Personnel: H. A. Fozzard, M.D., Medicine
F. M. Nolle, BCL
J. R. Cox, Jr., BCL

Institution: Barnes Hospital

Support: FR 00161
Washington University
Barnes Hospital

As a first step in the development of on-line computer diagnosis of cardiac arrhythmias (see A-6), the proper care facility for patients was required. In cooperation with Barnes Hospital and the Department of Medicine, a four bed intensive care nursing unit was established in Barnes Hospital for patients with acute myocardial infarctions or severe arrhythmias. Several basic ECG amplifiers and oscilloscopes were obtained from several manufacturers for comparative evaluation and modification. A central monitor for the nursing station was designed and built containing the termination of telephone lines for transmission (after frequency modulation) of the ECG signals to BCL. The signals were then available for the ECG monitoring project, and were also tape-recorded for routine analysis. A necessary part of the success of this project was the training of a highly skilled group of nurses to handle the early primitive monitoring equipment, to obtain adequate electrode handling for clean recordings, and to assist in the gradually increasing use of computer monitoring of the patients. The unit is functioning well, and teletype communications are being installed to keep up with progress in the ECG monitoring program.

8. Electrical Model of the Heart

Personnel: W. E. Long, B.S., Grad. Student, Electrical Engineering
J. R. Cox, Jr., BCL

Department: Electrical Engineering

Support: FR 00161
Washington University

The simulation of the conduction of electrical signals from the heart to the surface of the body could provide information useful in the interpretation of both normal and pathological electrocardiograms. To implement such a simulation, a plastic torso filled with a conductive medium is used. Voltages generated by the LINC will be applied to a silver plated model of the heart embedded in the torso. These voltages will simulate the depolorization waves that travel over the surface of the human heart.

The simulated heart consists of 162 separate electrical areas on the surface of a hard plastic material shaped like the human heart. The plastic torso has been obtained and a conducting solution simulating the resistivity of the human trunk is being evaluated. The digital and electronic circuitry needed for the interface between the LINC and the heart model have been designed and partially breadboarded.

9. Optimal Processing of Fetal Electrocardiograms

Personnel: L. Medgyesi-Mitschang, M.S., Grad. Student, Electrical Engineering
J. R. Cox, Jr., BCL

Department: Electrical Engineering

Support: FR 00161
NsG (t)-86

The problem of processing fetal electrocardiograms is examined as a multiple parameter, multiple observation, signal estimation procedure using the Bayesian point of view. An analytical model for the fetal signal process is proposed that is compatible with the dominant physical features of the problem and also permits an analytical solution. The fetal complex is characterized by a set of signal parameters which in turn are given by a set of estimator equations. Analytical solutions of these equations are derived via the Lagrange expansion and sequential estimation analysis. Possible generalizations of the results to the general estimation problem have also been investigated.

10. Stimulus Control PIU

Personnel: T. T. Sandel, Ph.D., Computer Research Laboratory
A. M. Engebretson, BCL

Laboratory: Computer Research Laboratory

Support: FR 00161
FR 00218

A data terminal plug-in-unit (PIU) has been designed for controlling the frequency and signal level of an audio stimulus. Each PIU contains a 12-bit buffer register, a 12-bit digital-analog ladder, a 7-bit buffer register, and a 7-bit relay attenuator.

Frequency control is achieved by using the output of the 12-bit ladder as an input to a voltage controlled oscillator. Using a Wavetek oscillator Model 105 or Model 111, a maximum frequency range of 20 to 1 can be achieved. Continuous control of the frequency range is provided on the front panel of the PIU.

Signal level is controlled by the 7-bit buffer register and attenuator. Each section of the attenuator is constructed on a separate printed circuit card which contains an attenuator pad, a magnetic reed relay, and relay driver circuitry. The present PIU has an attenuator with a minimum step size of 1/2 db.

11. Radioisotope Scanning of the Brain

Personnel: P. E. Stohr, M.D., Neurosurgery
M. M. Ter-Pogossian, Ph.D., Radiology
R. G. Loeffel, BCL

Department: Radiology

Support: FR 00161
Washington University

This project will utilize the LINC computer to aid in the mapping of organs and tissues of the body by radioisotope scanning, with primary interest in mapping the brain.

Residual radioactivity in the blood vessels overlaying the brain tends to blur and distort the scans. The LINC can improve the mapping resolution by subtracting from the brain scan a correction in the form of a similar scan in which an isotope, labeling only the blood cells, had been administered to the subject.

A 3 inch Picker Magnascanner is being modified to provide electrical analogs of the scan position coordinates, as well as of the radiation count rate. This information will be transmitted over telephone lines from the hospital radioisotope unit to a LINC computer at BCL.

12. Studies on the Physical Properties of the Pulmonary Vascular Bed

Personnel: L. J. Thomas, M.D., Anesthesiology
A. Roos, M.D., Physiology and Anesthesiology

Departments: Anesthesiology and Physiology

Support: HE 00082
FR 00161

A LINC program was written to analyze the relations between intra-pulmonary pressure and pulmonary blood flow. The pertinent data were obtained from the output of appropriate transducers attached to an excised cat lung which was perfused with cat blood at body temperature. The intra-pulmonary pressure was varied along a sinusoidal time course and flow and pressure were recorded. In a separate set of experiments on the lungs, the pressure applied to the outside of the lungs was varied along a sinusoidal time course. The transducer outputs were recorded on a Grass polygraph, and simultaneously on an Ampex tape recorder. This LINC program will be employed to study, among other things, the phase relation between applied pressure and blood flow at a variety of frequencies and inflation pressures. BCL has contributed to this work by providing instruction, consultation, and equipment needed for applying the LINC to data anlaysis.

13. Contour Representation of Response to Electrode Stimulus of the Central Nervous System

Personnel: R. R. Wright, M.D., Neurology
H. Agress, Jr., BCL

Department: Neurology

Support: FR 00161
Washington University

An experiment was conducted to study the response to electrical stimulation of various regions in the cortex of the cat. Response data were obtained on a rectangular grid with a spacing of 1 mm on the outer edges and ½ mm toward the center. A LINC program was written to calculate and display a contour line of equal response. Options include the ability to store, erase or repeatedly display the contour (with the use of a storage scope) and directly locate and display the area of maximum response.

V. RESEARCH PROJECTS

D. Computational Applications

The following research projects are primarily computational in nature and often make use of existing computational techniques. The work was carried out by laboratory staff members using the facilities of the Washington University Computation Center.

The investigator responsible for the project is listed first. Biomedical Computer Laboratory staff members collaborating with this investigator are listed on succeeding lines.

1. Plasma Cell Grain Counts

Personnel: S. L. Clark, Jr., M.D., Anatomy
G. S. Whitlow, Jr., BCL
D. R. Franz, BCL
R. M. Hesse, BCL

Department: Anatomy

Support: GM 07176
G 22296
Washington University

Plasma cells were incubated in a solution of radioactive protein for various time lengths, then fixed, cut and treated with photographic emulsion and developed. Size of the cell nucleous, Golgi apparatus, and endoplasmic reticulum were obtained from enlargements. Silver grains were counted as a measure of radioactivity.

Ratio estimates and confidence limits of these estimates using Feller's Theorem were calculated for grains/weight and other ratios.

Publication:

S. L. Clark, Jr., "The Synthesis and Storage of Protein by Isolated Lymphoid Cells, Examined by Autoradiography with the Electron Microscope". Submitted to the American Journal of Anatomy.

2. Regulation and Bionucleic Acid Synthesis

Personnel: D. E. Kennell, Ph.D., Microbiology
G. S. Whitlow, Jr., BCL
D. R. Franz, BCL

Department: Microbiology

Support: GM 09830
G 22296
Washington University

This project, concerned with magnesium starvation of Aerobacter aerogenes, investigates nucleic acid and protein metabolism in A. aerogenes cultured in Mg++ -free medium.

In the majority of the experiments, the simultaneous incorporation into macromolecules of precursor molecules containing both (^{14}C) and (^{3}H) isotopes was studied. This results in an increased resolution of the biochemical problem as well as giving the same information in one experiment which would have required two experiments had only one isotope been used. Samples are counted in a scintillation counter. To make the corrections for channel overlap, background subtraction, etc. for 150 samples (approximate number from three sucrose gradients plus controls) requires approximately 40 hrs. when done by hand. The computer program makes these calculations and plots the resultant counting rate for each sample in less than two minutes.

Publications:

D. E. Kennell, "Use of Filters to Separate Radioactivities in DNA, RNA and Protein," Methods in Enzymology, In press.

D. E. Kennell, "Magnesium Starvation of Aerobacter aerogenes. I, II, III, IV", Submitted for publication.

3. Processing Audiometric Data

Personnel: J. D. Miller, Ph.D., Central Institute for the Deaf
G. S. Whitlow, Jr., BCL

Institution: Central Institute for the Deaf

Support: NB 03856
G 22296
Washington University

This program converts audiometric-threshold data from attenuator settings to sound pressures and then finds the means, and sums of squares of interest. During the past year the program was modified from that of "test status" to "production status" and production runs are currently being made.

4. Operating Characteristic Analysis

Personnel: J. D. Miller, Ph.D., Central Institute for the Deaf
G. S. Whitlow, Jr., BCL
R. M. Hesse, BCL

Institution: Central Institute for the Deaf

Support: NB 03856
G 22296
Washington University

In the analysis of evaluative processes in speech communication it is helpful to compute the "receiver operating characteristics." A program is in operation that uses the listener's predictions of the accuracy of speech communication events to compute measures of the correctness of the predictions.

Within the past year, minor changes have been made to the program (some revisions are still in process) allowing for more efficient processing of vast amounts of input data. A small addition was made to the existing program, which computes the trapezoidal areas under the operating characteristic curve.

5. Noise Produced by Random Molecular Motion in the External and Middle Ear

Personnel: A. F. Niemoeller, D. Sc., Central Institute for the Deaf
G. S. Whitlow, Jr., BCL

Institution: Central Institute for the Deaf

Support: NB 03856
G 22296
Washington University

An electrical analog of the external and middle ear is being used to study the velocity of the stapes at the end of the ossicular chain in the middle ear. This velocity is produced by random molecular motion in the lossy elements in the system determined by the external and middle ear. It is hoped that information about absolute hearing acuity can be obtained by hypothesizing that auditory threshold is determined by masking noise generated within the hearing system and by attempting to test this hypothesis in the manner described above.

The digital computer has been programmed to compute complex impedances and admittances at various points in the external and middle ear and to compute the resultant noise velocities and pressures at these points. In particular, the noise velocity at the stapes will be computed and compared with that velocity which is produced at the stapes when the ear is excited by threshold sound pressure levels.

To date, two separate mathematical models have been constructed, programmed, and tested using the IBM 7072. The first model failed to give meaningful data. The second model, although showing a considerable improvement over the initial model, has indicated that some revisions will be necessary. A third model is presently being formulated in order to examine some of the ideas suggested by previous attempts.

Publication:

K. K. Charan, J. R. Cox, Jr., A. F. Niemoeller, "Evaluation of New Couplers for Circumaural Earphones", J. Acoust. Soc. Am., 38: 945, 1965.

6. Antibody Response to Defined Antigenic Determinants

Personnel: C. W. Parker, M.D., Medicine
G. S. Whitlow, Jr., BCL

Department: Medicine

Support: AI 04646
G 22296
Washington University

This research is in the general area of hypersensitivity and antibody specificity. It involves the study of drug allergy in man and hapten specific responses in lower animals. This project utilizes fluorescence quenching and fluorescence enhancement to study the antibody hapten reaction, the quantitate antibody, the distribution of antibody in various immunoglobulin fractions, and antibody proteolysis. The fluorometric titrations involve adding increasing amounts of ligand to an antibody solution and following changes in fluorescence.

Calculations involve corrections for solvent blanks, protein blanks, dilution of bound hapten, etc. The computer program greatly facilitates these calculations and gives the required data.

7. Variability of Trace Metals in Human Livers

Personnel: H. M. Perry, M.D., Medicine
B. Hixon, B.S., Medicine
G. S. Whitlow, Jr., BCL

Department: Medicine

Support: AM 07507
G 22296
Washington University

Amounts of fourteen trace metals at different sites in human livers were measured and statistical analysis by the computer was used to determine the significance of the metals and/or of the sites selected. The analysis was performed using a standard analysis of variance subroutines available as a software item for the IBM 7072.

8. Retrieval and Analysis of Data Regarding 250 Patients with Carcinoma of the Lung

Personnel: Wm. E. Powers, M.D., Radiology
M. W. Brown, M.D., Radiology
G. S. Whitlow, Jr., BCL
D. R. Franz, BCL

Department: Radiology

Support: CA 5139
G 22296
Washington University

The computer facilities are being used to evaluate data obtained from 250 cases of carcinoma of the lung. The patients are under radiation therapy, and the clinical characteristics of each patient's tumor, the therapy applied, and the response evoked are evaluated to determine the characteristics of the type of lesion most responsive to treatment by radiation methods. Evaluation of the data provides, in addition, information about the ultimate survival of a patient with a given type of tumor.

Retrieval and analysis of data as well as separation of patients into syndromes or response patterns is done by computer.

9. Retrieval and Analysis of Tumor Patient Records on an Investigational Series of Patients with Malignant Head and Neck Tumors

Personnel: Wm. E. Powers, M.D., Radiology
L. A. Palmer, M.D., Radiology
G. S. Whitlow, Jr., BCL
D. R. Franz, BCL

Department: Radiology

Support: CA 5139
G 22296
Washington University

Over 300 patients with advanced head and neck cancer have been treated with radiation therapy as a planned preoperative measure. Detailed records suitable for computer recordings have been kept. These records, mainly on IBM cards, include the characteristics of the primary lesion, the clinical aspects of metastases, the radiation therapy method, the operative procedure, the pathological findings, the primary specimen, the metastases, the patient complications and follow up.

As an initial step, a protocol was mapped out depicting the parameters which would be pertinent for this study. The format for data coding sheets was then designed and applicable patient records abstracted. These records are being tested for a correlation of the factors that appear to be of significance in patient response to the combined method of treatment.

10. Pharmacological Activity and Electron Structure of Drugs

Personnel: R. L. Schnaare, Ph.D., St. Louis College of Pharmacy
G. S. Whitlow, Jr., BCL

Institution: St. Louis College of Pharmacy

Support: G 22296
Washington University

The relationships between the electronic structure of drugs and their pharmacological activity are being studied. Electronic structure is calculated theoretically by a quantum chemical technique, more specifically, the LCAO-MO method employing the Huckel approximations with neglect of overlap. The objective covers four basic areas of interest:
1) Determination of which electronic parameters are responsible for a drug's activity; 2) Determination of how electronic properties enable a drug to cause a particular pharmacological response; 3) The prediction of pharmacological activity of a given organic compound from basic chemical structure; and 4) The design of more specific and more efficient medicinal agents.

The heart of the program consists of obtaining the eigenvalues and eigenvectors of a real symmetric matrix. The matrix corresponds mathematically to the chemical structure of an organic compound. The remainder of the program consists of subroutines using the eigenvalues and eigenvector matrix to calculate parameters corresponding to electronic properties of the compound. The calculated properties include electronic energy levels, total pi electron energy, electron density, orbital densities, superdelocalizability indices both electrophilic and nucleophilic, bond orders, and orbital orders. All the atomic indices are calculated for both the total electronic or orbital population and for each of the three highest occupied or lowest empty electronic levels.

The main program, which computes eigenvalues and eigenvectors of a real symmetric matrix, was obtained from outside sources and modified for use on the IBM 7072. The subroutines listed above were written by BCL within the past six months with the design of test problems and debugging nearing completion.

11. The Relationship between the Mammalian Cardiac Action Potential and Contraction Strength under Varying Physiological Conditions

Personnel: Wm. W. Sleator, Jr., Ph.D., Physiology
F. S. Letcher, B.A., Medical Student
R. M. Hesse, BCL

Department: Physiology

Support: GM 1608
Washington University

Experiments were initiated last year to measure the transmembrane action potential of single cells in mammalian cardiac muscle. These experiments and partial analysis have been completed. The time integral of action potential

between specific voltage limits seems to correlate with contraction strength. Contraction strength seems to correlate, also, with the integral of all action potentials which occurred in the previous 5 to 10 seconds.

The data, originally stored on LINC tape, were transferred to IBM tape by means of a LINC program. The data are now ready for comparison with various mathematical models on the IBM 360/50.

12. Biometry of Colonic and Rectal Neoplasms

Personnel: J. S. Spratt, Jr., M.D., Surgery
G. S. Whitlow, Jr., BCL

Department: Surgery

Support: CA 09741
G 22296
Washington University

The purpose of this study is to collect data on the biological behavior and characteristics of benign and malignant colonic neoplasms in over 4,373 cases at Barnes Hospital and Ellis-Fischel State Cancer Hospital. All data are classified in an IBM punch card system and analyzed for the inter-relationship of the biological parameters of the tumors, i.e., growth rate to histology, multiplicity of tumors, rate of development of new tumors, relationship of histology and size to metastasis, and numerous others. Other biological factors, that is, genetics, associated diseases and so forth that might correlate with the development of colonic neoplasms, are also being investigated and the biological behavior of all types of colonic noeplasms are being determined.

The entire experience with colorectal carcinoma seen at the Ellis-Fischel State Cancer Hospital from 1940 through 1961 has been completely reviewed, and all the clinical and pathological variables have been tabulated on IBM cards. Follow-up is complete on this entire patient experience through 1964. Over 600 different clinical variables are being evaluated.

Processing of the data on colorectal carcinoma in the tumor registry at Barnes Hospital is now complete, and these data have been transferred to punched cards for analysis. One interesting facet of this analysis will be a consideration of the influence of individual surgeons on the long-term results with the treatment of colorectal carcinoma. Prospectively, a more refined system for the automation of the registry has been developed. This system is designed to achieve complete compatibility with a cooperative program that is developing among all the tumor registries in the state of Missouri, entitled "Missouri Cooperative Tumor Registry". Futher modifications, refinements and stream-lining are being undertaken. The experience derived from this project is likely to be used in the automation of the registry system at the Ellis-Fischel State Cancer Hospital.

Publication:

J. S. Spratt, Jr., "Incidence of Multiple Primary Cancers per Man-Year Follow-up", Submitted to Annals of Surgery.

E. Special Project

During the past year a special project with national implications has taken shape as the result of collaboration between BCL, the Computer Research Laboratory and the Department of Radiology. The research aspects of this work have been described elsewhere in this report (see A-1, A-11, A-12, A-15, A-16, B-9 and B-10). A description of other developments follows.

1. Radiation Treatment Planning Project

Personnel:
J. R. Cox, Jr., BCL
W. A. Clark, Computer Research Laboratory
T. L. Gallagher, BCL
V. W. Gerth, Jr., BCL
W. F. Holmes, BCL
W. E. Powers, M.D., Radiology

Support:
FR 00161
FR 00215
FR 00218
IBM Contract
Washington University

The advantages of the use of the Programmed Console (PC) in therapeutic radiation treatment planning were recognized early by radiologists at Washington University and by NIH staff. It seemed that other therapists active in the use of computers for treatment planning might find the PC of great assistance. With the aid of special funds made available to BCL (FR 00161 and FR 00215) and the Computer Research Laboratory (FR 00218), a special project to supply Programmed Consoles to teams from five different institutions was initiated in the fall of 1965.

A board of advisors selected four institutions in addition to Washington University. Radiation therapists and physicists at each of these institutions have been active in the use of computers in treatment planning. They are:

M. D. Anderson Hospital and Tumor Institute, Houston, Texas
Dr. F. Y. Durrance
Dr. Robert J. Shalek

University of Maryland School of Medicine, Baltimore, Maryland
Dr. Fernando G. Bloedorn
Dr. J. Eugene Robinson

Ontario Cancer Institute, Toronto, Canada
Dr. W. D. Rider
Dr. J. R. Cunningham

Temple University Hospital, Philadelphia, Pennsylvania
Dr. Robert Robbins
Mr. K. C. Tsien

On February 17 and 18, 1966 a two-day meeting was held at Washington University to describe plans for the use of the PC in treatment planning. Teams from each of the four participating institutions attended as did interested observers from the National Cancer Institute. At this meeting the directions of our work during the spring and summer were shaped by discussions between radiation therapists, radiation physicists, computer programmers and computer designers.

In March the final design of the PC was completed incorporating changes stimulated by the February meeting. Three computer manufacturers were asked to bid on the construction of five Programmed Consoles: Conductron Corporation, St. Charles, Missouri; Data Machines, Inc., Newport Beach, California; and Spear, Inc., Waltham, Massachusetts. Spear, Inc. was the low bidder with a per unit cost of $22,000 and a contribution toward engineering costs of $20,000. The total engineering costs are shared between the manufacturer and the purchaser.

The production version of the PC will use integrated circuits (Motorola Emitter Coupled Logic) and be housed in a cabinet two feet square and 30 inches high. A display scope, keyboard, position transducer and data storage device will be placed on a nearby desk top. Debugging of the production machines is due to begin the last week in July, 1966.

VI. TRAINING ACTIVITIES

During the year three short courses in programming the LINC, two FORTRAN courses, and one course in programming the Programmed Console were offered. Staff members and students attending were:

LINC October, 1965

R. Abbott	Computer Research Laboratory
M. Bhide, B.S.	Computation Center
R. Blocher, B.S.	Computation Center
L. Brock, B.A.	Ophthalmology
L. D'Agrosa, Ph.D.	Physiology, St. Louis University
J. M. Enoch, Ph.D.	Ophthalmology
J. P. Ferguson, M.D.	Neurology
H. A. Fozzard, M.D.	Medicine
L. Harth, B.S.	Pediatrics
D. C. Hellam, M.D.	Medicine
K. Kleinmann, M.A.	Psychology
R. McAllister, B.S.	Ophthalmology
J. P. Miller, B.S.	Computation Center
R. Miller, B.S.	Yalem Computer Center, St. Louis University
R. A. Moses, M.D.	Ophthalmology
J. A. Mulligan, S.J., Ph.D.	Biology, St. Louis University
P. Noll	Engineering
J. O'Flaherty, M.D.	Neurology
G. Schonfeld, M.D.	Metabolism
S. C. Stevens, Ph.D.	Biochemistry
P. E. Stohr, M.D.	Neurosurgery
J. W. Studt, B.A.	Physiology
G. Sturmfols, B.S.	Psychology
R. F. Sullivan, B.S.	Yalem Computer Center, St. Louis University
J. R. Turtle, M.D.	Metabolism
J. C. VanGilder, M.D.	Neurology
W. White, B.A.	Clinical Chemistry

LINC April, 1966

S. E. Asnis	Medical Student
M. E. Dodge, B.S.	Medical Student
L. M. Kotner	Medical Student
S. P. Londe, M.D.	Surgery
G. C. Oliver, M.D.	Cardiology
M. A. Tinell, B.A.	Pediatrics
L. J. Thomas, M.D.	Anesthesiology

FORTRAN May, 1966

S. E. Asnis	Medical Student
M. E. Dodge, B.S.	Medical Student
L. M. Kotner	Medical Student
L. J. Thomas, M.D.	Anesthesiology
P. E. Stohr, M.D.	Neurosurgery

LINC June, 1966

H. Agress, Jr.	BCL
A. Blum, M.S.	Computer Research Laboratory
D. A. Brown	BCL
L. Bubb, M.S.	Computation Center
D. F. Dierberg	BCL
D. Henderson	Central Institute for the Deaf
R. Hirsh	Computer Research Laboratory
S. P. Kahn	BCL
P. J. Kirwin	BCL
R. G. Loeffel	BCL
G. O. Stone, B.S.	Computer Research Laboratory
P. L. Talmage	BCL
E. Van Patten	BCL
D. Velten	BCL
T. Wadhwa	BCL
C. S. Watson, Ph.D.	Central Institute for the Deaf

FORTRAN June, 1966

H. Agress, Jr.	BCL
D. F. Dierberg	BCL
R. Ganessan	BCL
S. P. Kahn	BCL
P. J. Kirwin	BCL
P. L. Talmage	BCL
T. Wadhwa	BCL

Programmed Console June, 1966

H. Agress, Jr.	BCL
D. A. Brown	BCL
L. Bubb, M.S.	Computation Center
D. F. Dierberg	BCL
S. P. Kahn	BCL
P. J. Kirwin	BCL
P. L. Talmage	BCL
E. Van Patten	BCL
D. Velten	BCL
T. Wadhwa	BCL

VII. PUBLICATIONS

Publications and papers presented or submitted during the period covered by this report are listed below.

J. R. Cox, Jr., V. W. Gerth, W. F. Holmes, "The Programmed Console: An Aid to the Radiologist in Treatment Planning", Presented at the International Conference on the Use of Computers in Therapeutic Radiology, Cambridge, England, 14th-17th June, 1966. To be published.

B. Walz, V. W. Gerth, W. E. Powers, J. R. Cox, Jr., T. L. Gallagher, "A Small Computer (Programmed Console) for Radiation Dosimetry Calculations", Presented at the 14th Annual Meeting, Association of University Radiologists, Little Rock, Arkansas, May 12th-14th, 1966.

J. R. Cox, Jr., "Special Purpose Digital Computers in Biology", Computers in Biomedical Research, Vol. 2, pp. 67-99, 1965.

J. H. Satterfield, "A System for Selection of Responses for Averaging", The Electroenceth. Clin. Neurophysiol., Vol. 21, Issue 1, pp. 86-88, June 1966.

W. E. Ball, R. I. Berns, "Automast-Automatic Mathematical Analysis and Symbolic Translation", Presented at the ACM Symposium on Symbolic and Algebraic Manipulation, Washington D.C., March 29-31, 1966. To be published in the Comm. of ACM, August 1966.

T. L. Gallagher, W. E. Powers, "Optimization of Radioactive Dose Rate Distributions for External Beam Sources", Presented at the International Conference on the Use of Computers in Therapeutic Radiology, Cambridge, England, 14-17 June, 1966. To be published.

T. L. Gallagher, W. E. Powers, S. J. Smith, "Implant Dosimetry Using the Programmed Console", Presented at the International Conference on the Use of Computers in Therapeutic Radiology, Cambridge, England, 14-17 June 1966. To be published.

R. A. Dammkoehler, "A Computational Procedure for Parameter Estimation Applicable to Certain Nonlinear Models of Enzyme Kinetics", The Journal of Biological Chemistry, 241, No. 9, pp. 1948-1957, May, 1966.

R. A. Dammkoehler, J. Ogura, et al., "Nasal Obstruction and the Mechanics of Breathing", Archives of Otolaryngology, 83 pp. 135-150, February, 1966.

R. A. Dammkoehler, T. L. Gallagher, "A Computer Program for Analysis of Fluorescence Quenching of Antibodies by Ligands", In Methods of Immunology, Vol. I, by H. N. Eisen and J. E. McGuigan, Academic Press, N.Y. In press.

J. M. Vanderplas, "A Method for Determining Probabilities for Correct Use of Bayes' Theorem in Medical Diagnosis", Submitted for publication.

S. L. Clark, Jr., "The Synthesis and Storage of Protein by Isolated Lymphoid Cells, Examined by Autoradiography with the Electron Microscope". Submitted to the American Journal of Anatomy.

D. E. Kennell, "Use of Filters to Separate Radioactivities in DNA, RNA and Protein", Methods in Enzymology, In press.

D. E. Kennell, "Magnesium Starvation of Aerobacter aerogenes. I, II, III, and IV", Submitted for publication.

K. K. Charan, J. R. Cox, Jr., A. F. Niemoeller, "Evaluation of New Couplers for Circumaural Earphones", J. Acoust. Soc. Am., 38: 945, 1965.

R. L. Schnaare, A. N. Martin, "Quantum Chemistry in Drug Design", J. Pharm. Sci. 54, 1707, 1965.

J. S. Spratt, Jr., "Incidence of Multiple Primary Cancers per Man-Year Follow-Up", Submitted to Annals of Surgery.

G. B. Cook, "A Comparison of Simple and Multiple Primary Cancers", Cancer, Vol. 19, No. 7, pp. 959-966, July, 1966.