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Washington University Computer Laboratories: A summary of accomplishments of the Washington University Computer Laboratories from 1967 to 1983

Washington University

Computer Laboratories

From 1967 to 1983

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A SUMMARY OF ACCOMPLISHMENTS OF THE WASHINGTON UNIVERSITY COMPUTER LABORATORIES FROM 1967 to 1983

A description of research results including a comprehensive bibliography covering work done at Washington University in the Biomedical Computer Laboratory and the Computer Systems Laboratory under a major grant from NIH entitled "A Resource for Biomedical Computing."

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Foreword

This document began as an abbreviated montage of earlier annual reports for NIH grant RR00396, entitled "A Resource for Biomedical Computing" which supported work at the Washington University Computer Laboratories from 1967 to 1983. The assembled collection of annual reports prepared under RR00396 constitutes a mass easily weighing thirty pounds. And while this mass of paper implies weighty research in both quantity and quality, only the stout-hearted would attempt to consult these documents to gain some sense of the work that has gone on under this grant.

The NIH grant RR00396 supported two laboratories and three adjunct activities, the Biomedical Computer Laboratory (BCL), the Computer Systems Laboratory (CSL), the National Collaborative Research Program (NCRP), the Information Systems Group (ISG), and the System Design Aid Group (SDAG), all within an administrative structure called the Washington University Computer Laboratories. The scope of work at the Laboratories has been wide-ranging. An eclectic and diverse group of scientists have pursued research across a host of disciplines and a comprehensive review of this work has not, until now, been undertaken.

We hope that this presentation will give the reader an overview of the broad scope of research that has been carried out here over this fifteen year period. It consists of an essay which covers the history of the laboratories and research projects that have received support from the grant, and a bibliography of the publications produced by the Laboratories and their collaborators from 1967 to 1983.

Acknowledgements

Many people have been generous with their time during the preparation of this document and space will not permit me to list them all. Drs. Lewis Thomas and Jerome Cox provided constructive criticism and often needed editorial advice. The researchers at BCL and CSL have been endlessly patient with my attempts to reduce highly technical projects to readable prose form and I am in their debt for the explosive dose of knowledge I received in doing so.

Don Hirsh

Summer 1985

Almost all of the compilation, editing and writing was done by Don Hirsh in 1984 and 1985 while he was on the staff of CSL. I give him my special thanks and also commend him for his fearlessness in undertaking the task of digesting the many documents and his ability to span the broad scope of the activities of the two laboratories. I thank Charles Molnar, Director of CSL, for allowing him to spend so much time on the project. After completing the manuscript, Don Hirsh left CSL, but meanwhile at BCL, Russ Hermes and Polly Raith were working on the bibliography. Russ wrote programs for the initial preparation of the bibliography and Polly, throughout 1985, spent what must have seemed an eternity typing it. Without their hard work this summary would be considerably reduced in value. I thank Russ, Polly and Lewis Thomas, Director of BCL, for their patience in seeing the bibliography through to the end.

As a result of my inattention, the project moved slowly until the approach of the 25th Anniversary Celebration of BCL and CSL on May 12, 1989. It seemed an appropriate year to publish this summary. Helping me to complete the job were Mary Rose Hoare (The Hague) and Ken Wong (St. Louis). Their editorial assistance has been valuable and effective. Finally, I must note my special thanks to Myrna Harbison who did the manuscript preparation through many revisions and over the last few years.

Reported in the pages that follow is a summary of work done at BCL and CSL up to 1983. Much has been accomplished at BCL and CSL since then that is not reported here. The interested reader may wish to consult "25 Years of Biomedical Computing at Washington University" by Charles E. Molnar and Lewis J. Thomas for a brief overview of the entire twenty-five year period.

Jerome R. Cox, Jr.

Summer 1989

1. Introduction

> In the beginning (about 30 years ago) when all computers were large and very expensive, they existed only in the inner sancta of the computer centers of large institutions. Most programs and data were carried to the computer in the form of punched cards and the line printer output was retrieved hours or days later. Then, at some point in the steady decrease in the size and cost of computers, the minicomputer entered the scientific laboratory. It enabled the computer to collect data directly from the instruments and also perform some limited data processing. This was the beginning of computers in scientific instrumentation, and for many scientists the "laboratory computer" became a new and exciting tool. When the computer was dedicated to a single instrument, it was able to control the instrument and perform the data collection process. Early applications of dedicated computers were all with costly instruments ..., but as computers continued to decrease in cost and size, so did the scale of instruments to which they could be dedicated. The last great leap in this evolution has been the incorporation of the remarkably inexpensive and tiny microprocessor to instruments of every type from spectrophotometers to balances and pH meters.
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> (Enke, C. G., "Computers in Scientific Instrumentation", *Science* vol. 215, 1982)

At Washington University, the Computer Systems Laboratory (CSL) and the Biomedical Computer Laboratory (BCL) have been at the heart of the changing scientific technique summarized in the preceding quotation. Few laboratories in the nation have had as deep an impact on the evolution of computers in medicine and medical research as CSL and BCL. A landmark in the history of biomedical computing at Washington University occurred with the formation of the Institute also coincided with the completion of a major fifteen-year grant from the Division of Research Resources at the National Institutes of Health (RR00396). Since 1967 this NIH grant has been the source of major funding for BCL, CSL and certain adjunct activities. With the synthesis of these laboratories and activities into a single administrative unit it seemed appropriate to summarize their work over the last decade and a half.

2. Overview of the WU Resource for Biomedical Computing

2.1. The Organization of Biotechnology Resources

In the early 1960s a number of large-scale resources were organized to facilitate the use of computing tools in biomedical research. Most of these resources were housed in major universities and funded, at least initially, by what was then known as the NIH Biotechnology Resources Program. The nucleus of the resource at Washington University was formed in 1964, when BCL was formally organized to focus on the biomedical applications of modular computing equipment and minicomputers. Most of the other early resources depended on and developed large computer systems because of the economies that could be achieved by many users sharing one central computer. The Health Sciences Computing Facility established by Wilfrid J. Dixon at UCLA is an example of this approach which has provided exceptional service to many biomedical researchers throughout the nation, especially in the statistical analysis of experimental or epidemiological data. Over the past 20 years, there has been a dramatic drop in the cost of computing so that relatively fewer users need to tie themselves to large computers to achieve their objectives. The kinds of problems that require a large mainframe computer for their solutions have diminished with the availability of powerful minicomputer and microcomputer systems.

2.2. Organization and Goals of the WU Computer Laboratories

The Washington University Computer Laboratories were organized in 1967 to include BCL and CSL. From 1964 to 1983 these two sister laboratories (and CSL's forerunner, the Computer Research Laboratory) occupied adjacent space on the Medical School campus, where BCL activities have concentrated on applying state-of-the-art techniques to medicine and biology, and CSL projects have focused on the development of advanced computer technologies and systems that are particularly suited to biomedical problems. A National Collaborative Research Program (NCRP) was added to the Laboratories in 1975 to support the replication and fielding of a CSL-developed molecular modelling system, the MMS-X (of the 40 to 50 high performance graphic systems being used in 1985 for molecular structure research worldwide, approximately 25 were located in North America and 11 of these were MMS-X systems). In 1976 the Resource was extended to include the Information Systems Group (ISG) which had been allied with the Department of Computer Science; in 1977 the System Design Aid Group (SDAG) centered in the Department of Electrical Engineering was also included. These adjunct activities have worked together primarily through informal arrangements, but under the auspices of an administrative federation called the Washington University Computer Laboratories (WUCL). Interschool connections like these were the forerunners of the new Institute, where new techniques for doing science have brought about unprecedented

levels of cooperation between scientists of every discipline.

The primary, long-term goal of the Laboratories has been and continues to be the advancement of biomedical research through the novel application of state-of-the-art computing techniques in both research and clinical settings. The style of the program has always stressed close, multidisciplinary collaborations between biomedical scientists, engineers, physicists and mathematicians — the complete gamut of professionals involved in the study of complex biological phenomena. The scope of activities has ranged from the theoretical development of general computer-engineering methods, to the design and construction of special systems for solving particular biomedical research problems, to the fielding of systems used in the national research community, to the commercial replication of many technologies developed by the Laboratories.

2.3. Laboratory Computing for Biomedicine

The Laboratories sought to develop solutions to problems that have been insoluble by conventional computing techniques by devising small, specialized computer systems that reside in the research environment. The traditional strength of the Laboratories have been in developing a "close coupling" between digital computing and diverse biomedical needs; the approach to a given problem has been multi-disciplinary and oriented more towards particular solutions for a particular researcher or research group than to the more general offerings of a traditional computing center. In developing such computer systems it is important to have frequent interaction with biomedical scientists. Accordingly, research and development generally began with research collaborators in the Washington University Medical Center. Later the new theoretical and technical developments might be extended, through national collaborative programs, to serve the needs of other investigators at other institutions. Developments have also been exported through commercial collaborators.

Every new project undertaken by the Laboratories resulted in new capabilities for making measurements and observations or for manipulating information, enabling formerly impracticable studies to be conceived and carried out. New knowledge was generated in the fields of both biomedical science and computer engineering. With this new knowledge came the obligation to train people to work with it and to make this new knowledge available to other investigators and departments not involved with the Laboratories.

2.4. Training, Dissemination and Services

Knowledge in the biological sciences is exploding. This is no less true for the fields of computer science and electrical engineering. Accordingly, training is an important activity for the Laboratories. The Laboratories employ a select group of graduate students, primarily from Electrical Engineering and Computer Science, part-time during the school year and often full-time in the summer. Medical students also participate in and make important contributions to Laboratory projects. An important opportunity has been the increased collaboration among the Laboratories and the Departments of Computer Science and Electrical Engineering. This provides a great opportunity for students and faculty of these departments to have in-depth exposure to and involvement with biomedical computing.

Other training activities of the Washington University Computer Laboratories are directed to informing local and national scientific communities about specialized projects and facilities and instructing a broad spectrum of people in the application of advanced computer techniques to problems in clinical medicine and biological research. For example, over the past fifteen years more than 40 training courses have been offered without credit or charge by Laboratory personnel. Supported by University funds, the courses have covered a broad range of topics. A sampling of these courses includes programming, medical information systems, and most recently, an introduction to VLSI (Very Large Scale Intergration) techniques. More than 600 persons of diverse backgrounds have attended such offerings. Their numbers include physicians, medical and engineering students, graduate students, computer programmers, and technicians from departments throughout the Medical Center.

Laboratory developments that have general application are disseminated through publications, presentations, and personal contacts with colleagues at other institutions. As systems are developed, evaluated, and reported, investigators from Washington University and other institutions, as well as representatives from commercial firms, often inquire about securing the release of algorithms, hardware or software systems, or even complete systems. With few exceptions, such requests are granted.

As a consequence of our emphasis on tailoring small computing systems to particular research needs and applying such systems at the site of those needs, the service to users — as mentioned already — does not follow the usual computing center patterns. A traditional computing center in a university community is a facility that maintains one or more large main-frame computers and offers time-sharing services to the university at large on a fee-for-service basis. This is the basic structure of the Washington University Computing Facility. In contrast, the services of all the members of the Washington University Computer Laboratories are offered mostly to research collaborators. Other investigators seeking more general computing needs are guided to one of

several fee-for-service groups in the Washington University community. The Laboratories seek investigators with special problems that cannot be solved with the traditional offerings of computing centers. The laboratories offer all levels of involvement with collaborators ranging from the custom design of a new system to deal with a unique problem to consultation on purchasing commercially available equipment.

The Laboratories have been responsive to the general needs of the research community, however, by fostering the establishment of several unique facilities. The most recent of these was established in June of 1980 through cooperation with the Division of Biostatistics, the Washington University Computing Facilities, the Medical Computing Facility (MCF) and BCL. The result, the Medical Computing Services Group, offers general database services to the WU medical community. The Medical Computing Facility itself was spawned in 1975 by importing to BCL a small multiuser operating system. In the early 1970's a locally developed minicomputer (the PC 1200) and a then new operating system and computer language (MUMPS) were used in the experimental development of small medical databases. As these databases matured and their manipulation became routine, the MCF was formed and the Laboratories turned to more theoretical database studies.

2.5. The Future of the New Institute

The research program of the Washington University Computer Laboratories has received the greatest total funding of any activity ever supported by the Biotechnology Resources Program (now renamed the Biomedical Research Technology Program), and is recognized as the leading contributor to the development of laboratory computing systems for solving problems in biomedical science and for clinical applications. RR00396 has been a coherent source of funding for a diverse group of activities: wide ranging biomedical research, training, service and the general dissemination of new knowledge. The formation of the Institute for Biomedical Computing allows these activities to continue to take place, but under a more coherent administrative structure. The distinct organization and styles of both BCL and CSL will be retained, since they will remain as separate organizations within the Institute. The importance of the Institute is that it provides mechanisms and opportunities for both laboratories to take broader roles in teaching and research in the Schools of Medicine and Engineering, which in turn should improve the Institute's ability to identify and pursue new research initiatives. The immediate benefit to Institute personnel has been the addition of a fifth floor to Lopata Hall in the School of Engineering. Since BCL and CSL are both housed at the Medical School campus, broad interactions with engineering school faculty and students have heretofore been hindered, for no reason but that the Laboratories were out of the daily stream of events on the Washington University hilltop campus. The new space, which was first occupied in late

1983, provides Institute presence in proximity to engineering school faculty, students and research activities.

The formation of the Institute is recognition of the fact that the development and application of advanced computing and engineering technology to problems in biomedical sciences is an essential component of research and teaching activities of Washington University, and requires for its further development and continued stability an organizational structure that will accomplish the following:

(1) Provide a locus of primary academic affiliation that covers the broad range of interests that is inherent in biomedical computing;

(2) Establish a formal administrative connection to the School of Engineering and Applied Science that will facilitate the involvement of students and faculty in research and instruction in biomedical computing;

(3) Establish mechanisms for administration, funding, and review of appointments, promotions and tenure for the academic staff of this activity;

(4) Reduce organizational and procedural barriers between CSL and BCL by placing them within a common administrative structure; and lastly

(5) Create a focal point for interdisciplinary teaching and student research, both in the School of Medicine and the School of Engineering and Applied Science, in areas that do not fit comfortably into existing departments.

2.6. Summary

The goals of the new Institute for Biomedical Computing continue to be those of the Washington University Computer Laboratories from which it evolved:

(1) to be leaders in developing new digital computing technologies important to health-related research;

(2) to collaborate with biomedical scientists to address challenging research problems for which solutions can be found in the application of advanced computing techniques;

(3) to assist investigators in their application of computers to medicine by making Institute capabilities available to them;

(4) to train biological and physical scientists and engineers in biomedical computing;

(5) to develop, evaluate and field complete computing systems in both the local and national scientific communities; and

(6) to make this new knowledge available to the public in the form of improved diagnostic, therapeutic and research tools.

3. Minicomputers and Laboratory Computing Methods

3.1. Historical Background

Antecedents of the present Institute developed both in Massachusetts and Missouri in the late 1950s. In Massachusetts, Clark, Molnar and co-workers at Lincoln Laboratory developed the first digital averaged-response computer and applied it in neurophysiological research at MIT. Clark later designed the first minicomputer, building only two copies, but employing many features that would subsequently appear in the Digital Equipment Corporation PDP-5 (an early commercially produced minicomputer) and its descendent the PDP-8. In St. Louis, Engebretson and Cox, at the Central Institute for the Deaf, built the first version of HAVOC, a digital averaged-response computer especially designed for audiometry research.

From 1961 to 1963 a complete minicomputer system, the LINC (Laboratory INstrument Computer), was designed by Clark and Molnar for use in biomedical research. Lacking funds to replicate LINC in quantity, Molnar suggested (as a joke) that researchers who were interested in acquiring a LINC should come to their lab in Cambridge and build one. This bright idea led to the LINC Evaluation Program in the summer of 1963, where a dozen biomedical scientists assembled their own LINCs and transported them back to their home labs to apply them to research problems that included computer aided research in patient interviews, clinical laboratory automation, experimental physiology, neurophysiology and cardiology. In the following year Cox founded BCL at Washington University. A few months later, Clark and Molnar moved to Washington University to continue the LINC Evaluation Program and to establish the Computer Systems Laboratory.

The development of the LINC directly influenced small computer design. Firstly, Digital Equipment Corporation began commercially producing the LINC and later products were influenced by many of the LINC's design specifications. Secondly the basic configuration of the LINC has remained a de facto standard in the evolution of the microcomputer. The most common configuration of most of the now popular personal computers consists of a Cathode Ray Tube (CRT) display screen, keyboard, central processing unit, and a pair of floppy disc drives. But for the changing technology of building computers this is the configuration of the production LINC.

> While LINC contributed to DEC history primarily as a forerunner of the PDP-4 and PDP-5, it also generated a number of other developments. The LINC tape unit and the system ideas that permitted a user to have personal files were later incorporated directly into the DEC tape design and programs. The tape system and a powerful CRT-based console made possible the first complete personal computer available to a user, in this case the researcher, at a

> reasonable price.... On machines prior to LINC, DEC had been stressing design flexibility and modularity.... In contrast the LINC was quite constrained, with only 1 Kword or 2Kwords of primary memory available, two LINC tapes, and one CRT. By bounding the system to a single configuration, it was possible to provide a complete computing environment including software and to provide for convenient interchange of user software.
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> (C. G. Bell, J. C. Mudge, J. E. McNamara, *Computer Engineering;* Digital Press, Bedford, MA, 1978, pp. 175-176.)

3.2. Two Examples of Computers in a Laboratory Setting

The introduction of computers like the LINC into the research laboratory changed the scope and nature of experimental and clinical activity. Two examples will serve to illustrate this.

3.2.1. Automated Detection of Arrhythmias

Since 1906 when Eindhoven first recorded the electrical activity of the heart from electrodes attached to the skin, the Electrocardiogram (ECG) has become an important tool for the diagnosis of cardiac diseases. In this century, the ECG's importance has increased as a result of an epidemic of coronary artery disease caused by the diet, lifestyle and increasing lifespan of populations in industrialized nations.

Electrocardiographic signals are collected from electrodes placed at a number of different points on the body. The resulting set of signals conveys information about the electrical activity of the heart — the rhythmic depolarization and repolarization of the upper and lower chambers of the heart. The waveforms are traditionally recorded on paper and analyzed by an individual scanning the tracings for abnormal patterns. A trained observer can recognize abnormal shapes or timings associated with cardiac diseases. The associations of ECG abnormalities with specific cardiac abnormalities came through the accumulated experience of cardiology.

The uses of ECGs can be divided into two broad categories. First, short records of cardiac electrical activity spanning 30 seconds or less are used to detect the presence or absence of diseases of the heart muscle. These "diagnostic" ECGs require detailed interpretation by cardiologists, sometimes with the assistance of computer analysis. Secondly, because many diseases of the heart cause (often intermittent) potentially life-threatening derangements in cardiac rhythm (arrhythmias), much longer periods (24 hours or more) must be studied to detect and quantify those events which presage sudden death due to rhythm failure. These diseases require more rigorous diagnosis and treatment. Current estimates are that about half of all deaths due to cardiac disease are the results of arrhythmias. BCL's work with ECGs has focused on the

development of automated methods for rhythm analysis of long-term monitoring of ECGs. The ECGs either came from cardiac intensive-care units or from ambulatory patients outside the hospital. The long-term recordings are either captured on a small magnetic tape recorder and later analyzed at high speed, or analyzed continuously by a computer connected to chest leads, or by a tiny computer worn on the body.

Because long-term monitoring and high speed interpretation of ECGs by human observers is tedious and error prone, the reliability and untiring vigilance achievable with computers made them an attractive alternative. Furthermore, the increasing amount of ECG data to be analyzed was becoming a problem. Over the past decade there has been a three-fold increase in the number of diagnostic ECGs and more than a hundred-fold increase in the number of hours of arrhythmia recordings.

The recognition of abnormal ECG patterns on the part of humans requires skills and judgement which are difficult to emulate with computers. First, there is considerable variation among normal waveforms and in any given ECG there is often some form of background noise which can be confused with the electrical activity of the heart. Second, the variety of abnormal waveforms is very large and the variations are often quite subtle. Third, there is no consistent agreement among cardiologists on the interpretation of every waveform — so there are cases of waveforms which yield only probable categorization by the expert, whether human or computer. Consequently, automated arrhythmia detection programs, pioneered at Washington University and elsewhere, took more than a decade to develop and typically require up to 10,000 computer instructions. They represent one of the more complicated automatic pattern-recognition feats that has become a practical tool. The success of automated arrhythmia detection is the result of a number of sustained research efforts in computer science and engineering conducted over the past two decades. BCL's work in this field is described in more detail in 5.2.1.

3.2.2. Computed Tomography

Roentgen's discovery of x-rays in 1895 began a medical revolution. Within months x-ray shadowgraphs became a standard diagnostic tool. In 1972 Hounsfield's demonstration of computed x-ray tomography, a remarkable marriage of radiology and computer technology, started another revolution in medical diagnosis.

The modern digital computer is essential to this new imaging tool in a way not exceeded by any other use of computers in medicine. With millions of arithmetic operations the computer unscrambles the data from hundreds of projections of x-ray signals to produce a remarkably detailed image of a single section through the body. Such cross-sectional reconstructions have enough

spatial resolution and contrast to show tumors, vascular abnormalities and other lesions never seen before in such detail except at autopsy. It is as if the computer could slice through the patient with a magic blade that left no trace except to obtain the cross-sectioned image.

To understand the importance of this technique, consider the problem faced by the neurosurgeon who suspects the presence of a brain tumor, The x-ray-dense skull obscures the small difference in density between the fluid in the brain's ventricles and the brain tissue displaced by the tumor, making the shadowgram produced in a conventional x-ray examination virtually useless. To gain enough contrast to make the examination useful, the physician had to introduce air into the fluid filling the ventricles, performing what may be one of medicine's more painful procedures, the pneumoencephalogram. The decision to order the procedure was reached, particularly in the case of children, after exhausting all other diagnostic avenues.

Computed tomography, however, has a decisive edge over conventional radiography in its ability to show the subtleties of low-contrast tissues without interference from intervening body structures. Three years after its introduction, this new technique had nearly eliminated many invasive procedures, such as the pneumoencephalogram, and it has proven diagnostically more effective in many cases than any other noninvasive way of probing the body.

At Washington University, the extension of these tomographic techniques to nuclear medicine has opened new avenues for research and diagnosis. Whereas computed tomography using x-rays produces images of anatomy, the extension of these techniques to detect radioactively labeled molecules as they are metabolized by the body makes it possible to collect images of physiological and biochemical processes. For the first time, a physician can see and study an evolving heart attack or quantify the brain's use of energy-laden glucose. The Laboratories' development of PET is outlined in 5.2.3.

3.3. The Washington University Style

Over the years, the Resource has sustained a style and an approach to computers in research that was foreshadowed in the first averaged-response computers and embodied in the design of the LINC. This style employs a close coupling of small dedicated computer systems and the biomedical research laboratory or clinical laboratory. Also implicit in this approach is the requirement that the biomedical scientists become knowledgeable about the computers that are entering their laboratories.

Problems which demand the close coupling of the investigator or experiment to the computing system often require capabilities at the leading edge of digital hardware design. Multiprocessor systems and Very Large Scale Integration (VLSI) are now receiving the attention of biomedical computing

facilities dealing with such problems. Resources engaged in this study focus on the problems of representing information, distributed processing, high-performance digital communication and process coordination. The technologies are new but the design problems and goals are close to those addressed by the LINC program. Furthermore, many of the "modern" issues were encountered over a decade ago by the staff of CSL while designing and applying *macromodules* in the early 1970s.

4. Overview of Research in Biomedical Computing at WU

4.1. Introduction

This discussion will cover only the major research efforts of the Laboratories and these only in modest detail. There has been substantial intellectual activity at the Laboratories over the past fifteen years. The scope of the research runs the gamut from basic research into the fundamental properties of digital devices; to enhancing the ability of other laboratories to do basic biomedical research; to experimental clinical systems; to involvement in the commercial manufacture of clinical computing systems. The bulk of this section will be devoted to discussing the various projects and either commenting on their utility in the clinical or laboratory setting, or discussing the importance of the problem that a research program addresses. In several instances commercial electronics companies have become involved in the manufacture and marketing of ideas developed at the Laboratories. One of our missions has been to develop new knowledge, new systems and to disseminate these to the scientific community. The implicit assumption is that private companies often do not have the money to invest in basic research, but once an idea has borne intellectual fruit, a private concern can get the idea to the marketplace more effectively than a university. This flow of new biomedical knowledge into the marketplace benefits the whole population as scarce capabilities become replicated in the form of new machines and inventions. About half of the major research efforts outlined in Sections 4.2 through 4.5 resulted in commercial products. These university/corporate relations will be discussed in section 4.7, Commercial Ventures.

The research done at the Washington University Computer Laboratories falls into four broad categories:

(1) the development of computing capabilities, which includes the further development of the LINC, macromodules and VLSI;

(2) visualizing and studying physiological processes which encompassed electrocardiography, ultrasound, and tracer kinetics — a project which pointed the way to the development of positron emission tomography (PET);

(3) visualizing molecules and molecular processes — work which includes a national collaborative program in molecular graphics, and the development of a minicomputer-based mass spectrometer (both of these developments have had subsequent commercial production); and

(4) the general development of laboratory and clinical instrumentation which includes radiation treatment planning (for the treatment of cancer), the instrumentation of laboratories throughout the medical school complex, the instrumentation of medical and surgical intensive care units and the development of broadcast information systems.

More specifically, here is a list of major accomplishments during the past fifteen years. They are listed within the four broad categories outlined above.

4.2. Developing New Computing Capabilities

CSL's domain has been the development of new computing technologies. Although the variety of their projects was smaller than at BCL, many of their projects made far-reaching contributions to basic research in computer system design. These developments, which often did not have immediate impact in clinics or laboratories, have nevertheless had long term influence on developments in both the computer and biomedical sciences.

1964-73 LINC support:

Support of a national community of LINC users by preparing system documentation, developing major software, and installing several engineering changes. Detailed discussion of LINC support is not included in this report.

1964-73 Macromodules:

Development, design, construction and application of macromodules (MMs). Macromodules are a system of computer building blocks which allow an individual to rapidly assemble specialized (and therefore fast) computer systems without concern for most of the engineering details required for reliable operation (e.g., power, timing). After a sufficient inventory of macromodules had been built, a succession of over 60 widely different computers were constructed from that inventory.

1973-80 Restructured Macromodules:

Subsequent design, production and application of Restructured Macromodules (RMMs). The design goals of the RMMs were to reduce the cost and simplify the production of MMs. The principal success of MMs was their use in conjunction with stored program computers. RMMs, on the other hand, were designed to be permanently embedded in systems.

1980-83 VLSI:

Presently, Very Large Scale Integration (VLSI) circuit technology makes it possible to build semiconductor devices with hundreds of

thousands of transistors occupying a chip of silicon several millimeters square. This technology is responsible for the sharp decline in the cost of computing power that has occurred in the last decade. The prospect of creating custom chips for biomedical computing was the motivating force for the 1980 proposal to the NIH Division of Research Resources. The unique feature of this proposal was to apply ideas and expertise that developed along with macromodules to modular computer systems built with VLSI technology. The amount of circuitry that can be placed on a single chip, and the resulting increase in speed of execution, holds great promise for developing new computer-based tools in biomedical research.

4.3. Visualizing and Studying Biomedical Images

The term ***biomedical image*** is a catch-all to describe the information that can be collected about a physiological process and the method for displaying that information. For example, the activity of the heart can be measured as an electric signal that is roughly periodic and can be displayed on an oscilloscope. In this way one can study the electrical behavior of the heart over time. Another way to gain information about the heart is to take an ultrasonic ***picture*** which reveals much about the mechanical function of the heart in space and time. These two examples — waveforms and pictures — as well as other methods of measuring physiological processes are collectively addressed here as biomedical images. Accordingly, much of the work of BCL has been concerned with the acquisition, manipulation and study of biomedical images.

1964-83 ECG Analysis:

There has been a long-term involvement with the acquisition and processing of electrocardiographic signals. Work has ranged from design to commercial implementation of a minicomputer-based system for on-line arrhythmia analysis — analysis that is done as the patient is wearing the electrodes. Another method of monitoring is to make long-term recordings of a patient's ECG. BCL developed a system for the high-speed analysis of these long-term recordings. There is a continuing process of refining the algorithms for detecting and analyzing the arrhythmias.

1967-83 Auditory Physiology:

Experimental and theoretical studies of the nonlinear characteristics of the peripheral auditory systems of the cat were revealed by the discharge patterns of single cochlear nerve fibers. These studies were

used to formulate mathematical and physical models of the cochlea.

1968-83 Nuclear Medicine:

The physiological and biochemical manifestations of a disease can be studied by administering a radioactively labeled compound to a patient and following its course through the body by means of nuclear imaging instruments to detect the distribution of the radioactivity. The gamma camera and the Positron Emission Tomograph (PET) were developed in the late 60s and mid-70s, respectively, based on the regional detection of radioactively labeled compounds. BCL has been a pioneer in developing techniques for the computer processing of gamma camera images; in developing a series of PET systems; and in the continual refinement of image-reconstruction algorithms.

1976-83 Ultrasonic Imaging:

BCL collaborations with the Department of Physics and the Division of Cardiology have been addressing methods for the quantitative characterization of tissues — is it alive, or is it dead — using the techniques of reflected ultrasound and ultrasonic tomography.

4.4. Visualizing Molecules and Molecular Processes

The objects of study for the biochemist and molecular biologist are complex structures only nanometers wide. These scientists have always studied these objects by manipulating models, and by studying molecular structure by inference. MMS-X represents a case of the former and mass spectrometry a case of the latter. In the modelling of biological molecules, mechanical models can become prohibitively large and cease to be of use to the researcher. Such models of even simple biological molecules can take up many tens of cubic feet of space and are difficult to study. The development of molecular graphics has allowed the construction and visualization of complex molecules on computers with powerful graphics capabilities. In mass spectrometry, the behavior of ionized molecules in the presence of a magnetic field has yielded much information about the molecular composition of complex biological molecules, and the addition of minicomputer control has brought even more powerful capabilities to the laboratory.

1969-83 Molecular Graphics:

The MMS-X, a computer-based molecular modelling system, and the National Collaborative Research Program (NCRP) in molecular

modelling and graphics developed out of a succession of experimental systems. The first of these systems was constructed out of a LINC and a collection of some seventy macromodules. These systems have allowed molecular biologists to prepare and study three-dimensional representations of complex molecules — a system of modelling that is much more powerful than previous methods for visualizing molecular structures.

1969-75 Mass Spectrometry:

The combination of a gas chromatograph and a mass spectrometer has become a powerful tool in biomedical research. Gas chromatography is the fastest and highest resolution method for separating mixtures derived from tissues and body fluids, while mass spectrometry is a highly specific method for analyzing molecular composition. The interconnection of mass spectrometer and minicomputer has yielded an instrument capable of detecting picomolar concentrations of chemical compounds within a sample. The mass spectrometry program at Washington University has become a separate BRP Resource.

4.5. Development of Research and Clinical Tools

Most of the projects discussed so far are really concerned with the development of new tools for the biomedical community. That they fall into broad classes, such as *visualizing biomedical images*, makes their classification an easier task. But an impressive number of tools do not fall into one of the three categories mentioned thus far. Such projects constitute a fourth category: the development of research and clinical tools.

1967-83 Radiation Treatment Planning:

In radiotherapy, a specified volume of cancerous tissue in a patient is exposed to high-energy radiation in such a way that the tumor cells are destroyed selectively, leaving the surrounding healthy tissues relatively unharmed. BCL was responsible for the development, field trial, evaluation and dissemination of a minicomputer based system for radiation therapy planning. More recent work uses new information from computed tomography, advances in the understanding of the interaction of matter and radioactivity, and the power of VLSI circuits to advance the precision and clinical effectiveness of radiation treatment planning.

1971-77 Health Care Technology:

The showpiece of this line of research has been the design, construction, installation and evaluation of a high-performance minicomputer-based monitoring system for the Barnes Hospital cardiothoracic Surgical Intensive Care Unit.

1967-83 Broadcast System Development:

The broadcast system was conceived as an inexpensive and practical way to rapidly distribute large collections of programs and data from a central memory/transmitter to an unlimited number of specially equipped computer/receivers. An experimental implementation of such a system using cable television equipment was constructed with university support. The system was used primarily to give a computer administered version of the National Institute of Mental Health Diagnostic Interview Schedule. Within the past several years there has been a renewed interest in the broadcast system as a vehicle for the delivery of home-based computer services.

1967-83 Information Processing Research:

There has been long term study of the problems of collecting and studying information for statistical study, analysis and patient record maintenance. The development and use of MUMPS for the construction of databases in the early 1970s and the later development of the Information Systems Group are but two specific instances of work toward a solution of this long-standing problem.

1967-83 Speech and Hearing:

A longstanding collaboration with the Central Institute for the Deaf, an affiliate of Washington University, has focused on the development of digital instrumentation for a broad program of research in hearing and deafness.

4.6. Other Projects

As previously mentioned, this report is not a comprehensive history of biomedical computing research projects. We are omitting discussion of several important projects. Here, at least, is partial list of those not discussed.

Visual Field Analysis
Autoradiograph Analysis

Physical Mapping of DNA
Cardiac Electrophysiology
Modelling of Physiological and Chemical Processes
Microprocessor Systems Development

4.7. Commercial Ventures

One of the goals of the Washington University Computer Laboratories has been to foster the commercial development of useful medical computer systems as an expeditious means for exporting developments to the biomedical community at large. The importance of these developments as a measure of laboratory activity became formally recognized and stressed beginning in 1974, when a section of the BCL annual report, labeled *industrial collaboration*, was introduced. Collaborations with private industry, both direct and indirect, have been going on since the founding of the two laboratories. In 1974 four separate projects were mentioned that involved the exportation of BCL/CSL generated knowledge into the industrial sector.

These collaborations have evolved into two basic categories: 1) the exportation of new and specialized knowledge into the commercial marketplace; and 2) the performance of services, specialized data analyses that are available only through the use of BCL generated tools. An example of the latter would be BCL's participation in several drug studies by analyzing collected tapes with the Argus/2H system for companies testing antiarrhythmic compounds. By 1983, no less than 14 different companies had been involved in capitalizing on knowledge generated by the laboratories. The great bulk of this expertise was developed under funding from grant RR00396. By category, these are:

(1) LINC:

The further development of the LINC, previously mentioned in this report, did not occur under RR00396 funding, but does represent a landmark in computer design — developed in a university setting and widely emulated in the computer industry. LINC kits were marketed by DEC, but only a few were sold. LINC-8 was a DEC product that used the PDP-8 production technology to produce a machine that could execute both PDP-8 and LINC code, and provide LINC-like interfaces. The PDP-12 was a later product following on the LINC-8. About 2000 of them were made and sold by DEC. The Spear Micro-Linc family was a direct descendant of LINC and executed LINC code. Lastly, the LINC tape drive had a very strong influence on the design of DEC-tape, a product that generated approximately seventy million dollars for DEC.

(2) ECG Processing:

In real-time and high-speed ECG processing four companies have utilized substantial portions of the BCL work. Mennen Medical, formerly Mennen-Greatbatch, developed the two generations of ECG monitoring systems based on algorithms and hardware developed at BCL. General Electric and Hewlett-Packard have used the BCL-generated algorithms in their ECG monitoring system. Recently, BCL personnel have worked closely with Biosensor Corporation to implement the Argus algorithms in a portable, real-time ECG analyzer.

(3) Tomography:

Starting in 1973 and lasting for 3 years, BCL staff worked in collaboration with engineers from the Picker Corporation to develop advanced techniques for image reconstruction using computerized tomography. This collaboration was a forerunner of the PET development effort and led to three university-held patents. Design techniques used in the various PET scanners have led directly to the systems sold by the three U.S. manufacturers of PET equipment.

(4) Interactive Molecular Graphics:

A St. Louis based company, Tripos, was formed in 1979 to produce and market an interactive molecular modelling system based on the CSL developed MMS-X. The company has been staffed largely by Washington University trained computer scientists and in all has sold 180 systems. In 1983, Tripos shifted to marketing a molecular modelling software package which runs on the DEC VAX/PS300 and other platforms. Since MMS-X was one of the first of a new generation of modelling tools for the biomedical community, many design features have been emulated by other entrants in the field.

(5) Computer-Controlled Mass Spectrometry:

Another St. Louis based company, Teknivent, was formed in 1976 to produce a computer-controlled mass-spectrometry system similar to those developed in the BCL mass spectrometry program. They are the leading producer of alternative computer systems for commercial mass-spectrometry systems.

(6) Radiation Treatment Planning:

In 1970, Artronix Inc. took over the production of the programmed console (PC) and assumed responsibility for the distribution of the Radiation Treatment Planning System (RTPS). More than 200 of these are in service worldwide. Additionally, DEC and AECL implemented a version of the RTPS on the PDP-8 and the PDP-11. Although Artronix is now out of business, a successor company, Computerized Medical Systems, Inc., continues to maintain and further develop these instruments.

(7) Intensive-Care Patient Monitoring:

Many unique features of the high-performance, minicomputer-based patient-monitoring system for the Barnes Hospital Cardiothoracic ICU, installed in 1973, were emulated in products offered by Midwest Digital and Hewlett-Packard.

5. Detailed Descriptions of Research Projects

5.1. Developing Computing Resources

5.1.1. Macromodules

Macromodules were developed to allow assembly and use of arbitrarily large and complex digital systems without knowledge or concern for the enginering details that must be correctly dealt with if systems are to operate reliably and correctly. Another design goal was to facilitate the construction of systems with concurrency — the simultaneous processing of information at several sites within the system. The structuring of concurrent computation is a powerful technique which has many applications in biomedical computing.

The modules implement operations from very simple ones such as storage or addition to complex operations such as matrix multiplication or line generation for display. Complete specification of a system to be constructed from macromodules requires only a flowchart showing the operations and the conditions for which they are to be performed, and a placement diagram showing the physical arrangement of the modules. No consideration need be given by the user to timing, loading, cooling, or power distribution. These logically irrelevant characteristics are automatically dealt with by the supporting framework, the connections and the module design. Each operation takes as much time as is required. If the size of a system is increased by adding modules, if cable lengths are increased, or if the word length of an operation is increased, the time for operations may increase but the system will continue to operate correctly. The user need only concentrate on the logic of his algorithm, not on the electrical details of its implementation.

Sequencing correctness is ensured by allowing each operation to start only after the operations which must precede it are finished and their output data values have been transmitted to every place that may use them. Control signals are routed parallel to the data signals so that if the path for a data signal is extended, the corresponding control signal path will be extended also, and the completion of the operation will be delayed to account for the additional time required for the data.

All signals are buffered, and connectors and supporting hardware are designed so that fan-out or maximum cable length cannot be exceeded by any interconnection of modules and cables. A preliminary design allowed cables to be extended by plugging them together head to tail, in the same manner as water hoses. Since this would allow arbitrarily long cables to be assembled, the design was changed to use the same connector at both ends of the cable so that the maximum cable length could be controlled by restricting manufacture to allowed lengths. In this case, convenience was sacrificed to ensure that the cable length restrictions could not be violated. All power and cooling requirements are provided by the supporting structure by merely inserting

modules into the structure.

Control for concurrency is provided by branch and rendezvous modules that initiate multiple operations after the completion of a single operation and that initiate an operation only after several preceding operations have completed. The system designer can use these branch and rendezvous modules to control sequencing of concurrent operations where warranted by a particular algorithm, thereby greatly decreasing the time required for computation. Although specific consideration of time is not required for the design of systems using macromodules, estimates of the execution times can be made. One of the principle advantages of macromodules is that systems can be constructed that perform computations much faster than if implemented on a general-purpose computer with comparable circuit technology.

Macromodule systems have been assembled and used for a wide range of problems including: pseudo-random number generation; FFT calculation; Markov process calculation; determining algorithm concurrency; Hadamard transform processing; a stack computer; electrocardiogram data-reduction; testing stereo vision in infants; minimizing boolean functions; feasibility testing of radiation treatment planning algorithms; and a series of four systems for display of stick figures of molecules, which evolved into the MMS-X display system. Most of these systems were assembled and tested in a few hours to a few days of time. The four display systems were assembled over a five month period and allowed the four different organizations to be tested and evaluated.

Many of these systems provided very impressive improvements in processing time over alternatives. The boolean minimization system operated about 400 times as fast as a similar algorithm implemented on a minicomputer.

Macromodule systems are faster than comparable general purpose computers for three reasons: 1) concurrency in the algorithm can be exploited; 2) the individual instructions and data paths can be tailored directly to the algorithm requirements; and 3) no instruction fetches are required because the instructions are wired directly into the system.

Since the instructions are wired directly into the system, the complexity of the algorithms that can be dealt with satisfactorily is limited, although adequate for many applications. Of course, a general purpose computer with some special purpose instructions can be constructed with macromodules and several have been assembled and used. In many cases, however, the optimum scheme is to use a general purpose computer to deal with the infrequent but algorithmically complex operations such as I/O and user interaction. The computer is used to initialize a macromodule system that implements the computationally intensive part of the calculation and to harvest the results of the computation.

CSL's experience with macromodules has brought about important insight into system concurrency, an increasingly prominent problem in the design of

biomedical computing systems. The ease with which macromodule systems can be specified has important implications for the design of VLSI integrated circuits. VLSI techniques promise to allow us to execute design projects of unprecedented scope with many designers working together on single systems. The small number of parameters necessary to describe the interconnection of the modules, or other circuits that utilize the same communication and control protocol, means that the design of separate modules can be carried out almost completely independently, an important characteristic when many different designers may be working on a single system.

5.1.2. VLSI for Biomedical Applications

Very Large Scale Integration (VLSI) technology for integrated circuits provides a means to implement systems for carrying out extremely complex computational tasks. The effective utilization of this technology is crucial to the effective solution of the most demanding biomedical applications. As particular computational problems in biomedical applications have become tractable due to improvements in algorithms and computational capability, there have been more demanding problems to take their place. Early problems such as histogram generation and computer control of simple experiments, are now routinely handled by any of a large number of commonly available systems. More recent applications such as image processing for computed tomography or manipulation and display of stick figures of molecules are also common today. Some examples of today's focus are reconstruction of three-dimensional isotope distributions from time-of-flight positron emission tomography, calculation of allowed molecule conformations for drug design, processing ultrasound data for tissue characterization, improved cochlear mechanical modelling, calculation of scattered radiation dose in inhomogeneous media, and others.

A number of applications using macromodules and custom designed systems have shown that by tailoring a system to a particular problem, the computation time required may be reduced by a factor of about one hundred, a dramatic improvement. Difficulties that have been encountered with this strategy have been the care, time, and attention required to successfully assemble systems from components, particularly when multiple copies are desired. Macromodules provide a solution to the time and care required, but are expensive, and cannot easily take advantage of the improvements in technology that continually provide cheaper and better components, unless almost continuous redesign of the modules is undertaken.

A closer coupling of the design at the application level to the capabilities of integrated circuits, while using the well developed and highly automated commercial integrated circuit manufacturing capability, will help mitigate the problems of manufacturing while taking advantage of the continuous improvements in integrated circuit manufacturing technology. To be successful,

however, the design effort must be decoupled from the detailed manufacturing process. Effort can then be concentrated on the system level requirements so those designers associated with the particular problem can influence the structure of the solution.

The capability to design VLSI circuits without close coupling to fabrication facilities, pioneered by Carver Mead at Caltech, allows small research organizations to effectively utilize VLSI technology. This is important both for the tremendous capability provided by custom-designed integrated circuits and because it helps to avoid the early rejection of ideas that may initially seem computationally infeasible. The knowledge that a very powerful technology exists, whose capability increases yearly, makes it easier to invest in the early speculation and consideration of ambitious ideas that may eventually lead to useful applications. The tremendous improvements in the speed, cost, power consumption, and capability of integrated circuits leads to circuits fabricated with hundreds of thousands of transistors at present, and should allow fabrication of individual circuits with many millions of transistors before fundamental limits to performance improvements are reached. Utilization of this technology will be necessary to effectively and economically solve complex computational problems in the future. The same dramatic reductions in computation time that were accomplished by macromodule systems tailored to particular tasks is achievable with integrated circuits tailored to particular tasks.

Because it is necessary to understand the strengths and weaknesses of any technology in order to exploit it, CSL began exploring the characteristics and implications of custom design of VLSI circuits. The initial effort involved one semester of half-time effort at Caltech by C. E. Molnar which included the shared teaching of a course in self-timed logic and the introduction at Washington University in 1978 of EE463, a course in integrated circuit design. This was one of the first five such courses in the United States and used preprints of the Mead and Conway textbook that has become such a standard in the VLSI community that it has been referred to at conferences as *the book*. The course has been taught every year since its introduction and now has a yearly enrollment of about 60 students.

Many of the ideas and concepts introduced and developed in the work on macromodules is applicable to VLSI design. The concepts of modularity and of specification by sequence rather than by time are extremely significant. As the size of individual components becomes smaller, it becomes more and more difficult to control the timing between widely separated parts of the same integrated circuit. Thus, specification and control of operations by sequence rather than by time becomes increasingly important as the size of components is reduced.

A number of circuits have been designed by Washington University students and staff members and fabricated as part of multi-project chips along

with circuits from other designers and organizations. Several copies of each chip design, fabricated and packaged, were returned to Washington University and tested. These include a digital-to-analog converter, several circuits to measure the reliability of flip-flops used as synchronizers, part of a TRIMOSBUS interface, a circuit for measurement of integrated circuit delays, a crosspoint switch element and others. The design of an integrated circuit for the calculation of radiation dose in inhomogeneous media has been undertaken. The computational requirements for this task are enormous and a system designed specifically for the required calculations seems the only practical means to produce results in a clinically useful time (see 5.4.1 for this application).

5.2. Visualizing Physiological Processes

5.2.1. ECG Processing

During the mid-1960's, researchers at BCL began investigating automated analysis of electrocardiographic (ECG) signals. Algorithms for ECG-event detection and classification attempted to mimic the electrocardiographer's analytic thought process. Like any human skill, the ability to interpret an electrocardiogram is acquired chiefly from experience. The process is heuristic and based on circumstantial evidence. The machine algorithms must be likewise heuristic to deal with a wide variety of ECG waveforms. ECG-event shapes, timing and superimposed artifacts vary over time in any single patient and are likewise variable from patient to patient. Each person has a unique signature in his or her electrocardiogram. These complexities defy the modelling of the ECG as a stochastic process. After careful study, the approach to algorithm development which emerged was to: collect a digital database of a wide variety of ECG waveforms; tune the algorithms to maximize detection and classification performances on that database; and make adjustments to the algorithm as new waveforms with previously unencountered phenomena expose remaining weaknesses.

By 1969, ARGUS (ARrhythmia GUard System), a real-time ECG analysis system monitored any 2 of 15 patients in the Barnes Hospital coronary care unit. ARGUS ran on the Washington University-designed programmed console (PC). The ARGUS rhythm-analysis algorithms consisted of three cascaded software processors: data reduction of a 500-samples-per-second ECG signal into a stream of variable-duration slopes and bounds, QRS detection plus feature extraction, and QRS clustering and classification. The algorithms detected normal complexes and the most serious abnormal complexes (such as premature ventricular contractions or PVCs). Remote terminals at two nursing stations permitted medical staff to display arrhythmia and heart-rate trends. In addition, ARGUS initiated chart-recorder write-outs at these stations if serious events (specified by medical staff) were detected by the system. A clinical

evaluation of ARGUS demonstrated 78% PVC detection with a 0.4% false-positive rate. During the early 1970's, Mennen-Greatbatch Company (later Mennen-Medical), New York, implemented the Argus algorithms in commercially-available monitoring systems. Collaboration with Mennen continued, but formal work in real-time ECG rhythm monitoring ceased at BCL. Subsequently, Hewlett-Packard adopted aspects of the Argus algorithm in the HP78220 computerized arrhythmia detector.

In 1971, however, the National Institutes of Health awarded Washington University a contract (later a grant) to investigate the natural history of patients surviving acute myocardial infarction. A major portion of this study of sudden death syndrome included the implementation of a computer system which would analyze 10-hour tape-recorded ECGs obtained from the survivors at periodic intervals. The ECGs were obtained on ambulatory recorders, which permitted patient mobility. The system, Argus/H (high speed), analyzed the recordings at approximately 60 times real-time. The Argus/H hardware consisted of: a macromodular ECG encoding scheme for archiving ECG waveforms on magnetic tape, an IBM System/7 computer which ran the Argus arrhythmia analysis algorithms, and miscellaneous devices for displaying and documenting events of interest. Argus/H analyzed several thousand ECG recordings for the Sudden Death study. Local interest in this tool spawned numerous other studies such as ventricular arrhythmias in patients on various antiarrhythmic drugs or in patients prior to and after coronary bypass surgery as well as studies correlating arrhythmias with infarct size and site estimation.

By the late 1970's, a second-generation high-speed system, Argus/2H, analyzed 2-channel, 24-hour ECG recordings for the Sudden Death study, numerous local studies, and two major multicenter trials. Argus/2H ran on dual DEC PDP-11/34 computers, permitting simultaneous digitizing and analysis or editing and archiving. Two Argus/2H systems served both operational needs and further algorithm development. The original Argus algorithms were enhanced with new QRS detection/delineation methods and improved QRS clustering and classification schemes, including excursions into the frequency domain. Performance of the algorithms rose to greater than 98% PVC detection rate. Collaboration with Mennen Medical was discontinued in 1983 but Dalhousie University, Halifax, and Erasmus University, Rotterdam, have implemented versions of Argus/2H. Biosensor Corporation, Minnesota, has implemented the Argus algorithms in a portable real-time analyzer.

5.2.2. Sensory Biophysics

One of the research applications of computing that had provided experience and motivation for constructing the LINC was the study of peripheral auditory mechanisms in the Communications Biophysics Group of the Research Laboratory of Electronics at MIT. Work in this area, originally

undertaken as part of the doctoral research of Drs. Molnar and Pfeiffer at MIT, was continued at Washington University by their establishing a Sensory Biophysics Laboratory located within the Department of Physiology and Biophysics, and supported jointly by that Department, the Department of Electrical Engineering, and the Biotechnology Resource.

Three purposes were to be served by this Laboratory. First, study of the peripheral auditory system was to be undertaken through a tightly coupled set of experimental and theoretical studies, making use of modern computing tools and current engineering concepts of communications and signal processing. Second, the Laboratory was to serve as a place in which students could be exposed simultaneously to technically and scientifically strong environments and advisors. Finally, the research and educational benefits of such a research style and environment were to be explored and demonstrated as models for research in other biomedical problem areas.

During their dissertation research, while Molnar and Pfeiffer dealt with experimental and modelling studies of the cochlear nucleus, it became clear that further quantitative study at that level of the auditory nervous system required a better understanding of the encoding of acoustic stimuli in the cochlear nerve itself. Current thought of the time envisioned the inner ear as consisting of a sharply tuned mechanical filter. This picture, while generally accepted, presented several dilemmas, including discrepancies in the sharpness of tuning of the filter and a difficulty in accounting for the very high sensitivity of cochlear nerve fibers to low-level acoustic stimuli.

Dr. Thomas Goblick, a colleague of Dr. Pfeiffer, conceived of an ingenious experiment intended to measure the sharpness of tuning of the cochlear filter through the study of the responses of individual cochlear nerve fibers to stimuli consisting of pairs of clicks whose relative timing and amplitude could be adjusted. To carry out this study, Goblick came to St. Louis for a year, during which a set of studies was completed that produced results at odds with the accepted view of the cochlea as a mechanically linear filter.

Much of the following work in the Sensory Biophysics Laboratory attempted to account for the inconsistencies revealed by the Goblick and Pfeiffer study, and to devise alternative hypotheses (in the form of quantitative models) for the linear filter interpretation. The dissertation work of Littlefield (1973) determined that there was a limited range of stimulus conditions under which cochlear nerve responses were consistent with a linear hypothesis, but that the range was narrow. Kim, in his dissertation (1974), proposed a set of coupled nonlinear differential equations that could reproduce a wide variety of nonlinear cochlear phenomena. Although these equations could not readily be identified with physiological mechanisms, they indicated strongly that the nonlinearity was associated with energy dissipating rather than with energy storing mechanisms such as compliance and mass.

Using Fourier analysis techniques developed by Pfeiffer and Molnar, Pfeiffer and Kim developed experimental techniques that permitted recordings to be made from hundreds of different cochlear nerve fibers in the same animal, thereby providing a means for simultaneously studying both frequency and position dependence of cochlear nerve responses. This technique, refined in the dissertation work of Siegel, and combined with careful histological examination, led to the conclusion that there were indeed important nonlinearities in the mechanical behavior of the cochlea, and that these nonlinearities were reduced or eliminated by a variety of different kinds of injury to cochlear mechanisms by such disturbances as intense noise exposure, surgical trauma, anoxia, or chemical poisoning.

These results conflicted with reported studies of cochlear microphonic responses, which claimed not to show significant amounts of response at distortion frequencies in regions remote from the stimulus. Gibian, in his doctoral studies, repeated and extended the previously reported work, and demonstrated the presence of distortion signals, as well as explanations of why they had not been seen in earlier studies.

These experimental studies demanded interpretation and rationalization in terms of cochlear mechanical models. Two students of Dr. Cox, Lien (1969) and Spenner (1976), developed a hydromechanical model of cochlear mechanics that permitted the introduction of nonlinear damping into the mechanical model for the behavior of the cochlear partition. The Spenner model, as extended by Matthews and Spenner, demonstrated the ability to generate traveling waves at intermodulation frequencies, and showed that they could propagate both toward the apex of the cochlea and backwards towards the middle and external ears.

Other work done elsewhere further confirmed the existence of mechanically-present distortion signals in the cochlea by showing that distortion frequency responses to paired tones could be found in the ear canal. Matthews (1980) in his doctoral dissertation, further extended the nonlinear cochlear mechanical models to demonstrate that distortion signals in both the apex of the cochlea and in the ear canal could be interpreted by the same model for their generation and propagation.

The observance of spontaneous acoustic emissions and of long-delayed cochlear echoes to acoustic stimuli by others strongly suggested that mechanically active as well as nonlinear phenomena were to be found in the cochlea. Kim, Neely, Molnar, and Matthews showed that a linear cochlear model including negative partition damping (indicating an active mechanism) produced sharp mechanical tuning. In his doctoral dissertation, Neely introduced a second degree of freedom into the cochlear motion at each point along its length, corresponding to several possible interpretations of the micro-mechanical processes taking place. Kim and Neely then showed, among other things, that it is possible for mechanical energy to be converted from other energy sources (such as metabolic), thereby increasing the cochlear mechanical

gain and sensitivity without rendering the overall system unstable.

These studies, taken together with work done elsewhere, have contributed to a major revision of the classical view of the cochlea as a passive and linear mechanical filter driving a complex and sensitive transduction mechanism. The new view that is emerging suggests a much more sophisticated and complex system, in which there is bidirectional coupling between successive stages in the process, and in which the active and nonlinear phenomena are pervasive and essential elements in the operation of the system. While the range and complexity of the hypotheses and models that must now be considered and evaluated is far greater than the simpler view of two decades ago, means for reconciling the paradoxes that could not be dealt with by earlier, simpler views appear to be at hand.

The current state of affairs calls for the design of new and more complex experiments, placing new demands on the researchers' ability to design, control, and produce acoustic stimuli; on the collection and analysis of experimental data from cochlear nerve fibers and gross electrodes; and on their ability to construct and test comprehensive mathematical and computational models incorporating their hypotheses. The design and testing of a new digital stimulus generator that is capable of producing a wide range of stimuli of high purity, given simple coded descriptions of the stimuli was completed in 1983. The dissertation work of Gaumond demonstrated a method of separating post-spike recovery factors from stimulus-dependent factors in the probability of a cochlear nerve spike discharge, providing a powerful tool for improving the usefulness of cochlear nerve studies as probes of intro-cochlear mechanisms. Construction of new and more comprehensive models extending mechanical models to include the bidirectionally coupled transduction mechanisms presented a challenge to the researchers' mathematical and computational skills.

Once again, Institute researchers were equipped with a set of hypotheses to test, a set of new experimental and analytical tools to use, and a technically and biologically advanced environment in which to do their research and train their students.

5.2.3. Nuclear Medicine

The possibility of using short-lived radionuclides, such as carbon-11, nitrogen-13 and others, for the assessment of physiological processes by tracing the course of radioactive compounds through the body has been recognized since the early 1940s. Because the half-life of these particular radioisotopes is quite short (all less than 1/2 hour) and the cyclotrons needed to create them were generally not located near medical research facilities, they were difficult to work with and were generally overlooked by investigators until the mid-1960s.

The short half-lives of these radionuclides and the difficulties involved in making external measurements of their distributions within the body were formidable barriers to their adoption in the laboratory. The first step towards the solution of these problems was taken in the mid-1960's, when cyclotron-produced, short-lived radionuclides were used in a series of in vivo biochemistry experiments conducted in a trailer adjacent to the Washington University Department of Physics. In 1963, with help from the NIH, the first cyclotron in the nation to be located in a medical center was installed at the WU School of Medicine. In 1978 a second cyclotron was built to respond to expanding research needs. Ingenious, rapid chemical syntheses were developed which permitted the use of these short-lived isotopes to label a large number of highly complex compounds. The accurate localization and detection of the extremely small quantities of radioactive material within the body remained a problem.

The development of Computed Tomography (CT) and the appearance of a commercial system by the British company EMI in 1972 stimulated collaborative studies between BCL and the Division of Radiation Sciences to assess positron coincidence-detection as a method of tomographic reconstruction. The series of Positron Emission Tomographic (PET) scanners are the results of these collaborations.

The development and significance of PET becomes clear when it is contrasted with the conventional imaging devices of nuclear medicine and with CT. In the former case, the use of the Anger Scintillation Camera provided somewhat distorted images of the distribution of radioactive isotopes. The problem with the Anger camera was its inability to distinguish the region of interest from the surrounding tissue; the images were essentially the mapping of three-dimensional volumes onto two-dimensional surfaces (researchers at BCL studied the problems of processing images from the Anger camera from the late 1960s to the early 1970s).

CT however, allows for the collection of accurate two-dimensional *slices* of density information from the body. But because the medium uses X-rays, no information about a specific physiological function can be obtained. PET scans can give a great deal of information about organ metabolism and physiologic function, whereas x-rays yield information about the structures of the body. However, by the time a pathological condition manifests itself in a CT scan, if ever, the underlying pathology is usually well advanced. Visualizing the same region of the body with a PET scan could likely reveal the condition before it would be manifest in an obvious structural aberration. Thus PET is the technique that combines the biochemical assessment of pathology achieved by nuclear medicine with the precise image reconstruction of computerized tomography.

Subsequent generations of PET systems continue to build refinements in data collection and in the spatial resolution of the images. One of the most exciting recent developments for emission tomography has come from crystal

technology and high-speed electronics. Advances in both of these fields now allows estimation of the differential time (in picoseconds) it takes for the radiation to travel from source to the detectors (at the speed of light), improving the quality of the resulting images. At CSL, engineers are currently designing custom VLSI hardware to be used in future generations of PET scanners.

5.2.4. Ultrasonic Imaging

When work on ultrasonic imaging began at BCL in the mid 1970's, ultrasound was already in use as a diagnostic tool. Results of examinations based on conventional ultrasonic methods at that time, however, were (and still are) primarily qualitative and pictorial. Ultrasound scans are a valuable, non-invasive procedure for visualizing the internal structures of the body, but do little more than generate the two-dimensional outlines of various organs. The notion of using ultrasound to distinguish between various tissue types has posed fundamental problems in the design of new and more sophisticated ultrasound equipment. In collaboration with the Division of Cardiology and the Department of Physics, a group of researchers from BCL have worked on methods for quantitative tissue characterization via ultrasound. The overall goal has been to use ultrasound for the non-invasive identification of tissue pathologies — to be able to distinguish dead heart tissue, tumors, cirrhotic regions of the liver and other abnormalities from normal surrounding tissue. For example, images of tissue properties would be invaluable in the diagnosis and treatment of coronary artery disease, where the ability of the heart to function normally has been impaired by the loss of blood supply to small regions of the myocardium. Such a loss of circulation can result in an infarct — a region of dead tissue.

A major step towards realizing this procedure occurred when an ultrasonic, tomographic scanning and image reconstruction system designed and built at the BCL became operational in February of 1977. The system was designed to allow tomograms to be performed on excised tissue suspended in water (ultrasound propagates more effectively in water than in air). Accurate two-dimensional images were produced which took into consideration the results of ultrasonic attenuation, phase velocity, and integrated backscatter. These experimental images were generated from tissue models and tissue samples. In 1979 the localized attenuation across slices of dog myocardium which contained experimentally induced infarcts, regions in which blood flow had been impaired, was quantified for the first time. The resultant images clearly showed the location and extent of the dead tissues.

In order to generate accurate images several sources of error had to be identified and appropriate corrections made to overcome their effects. The primary errors were due to reflection and refraction of ultrasound in tissue,

because of phase cancellation across the face of the receiving transducer. Simulations in which ultrasonic rays were traced from the transmitter to the receiver through tissue showed the relative magnitudes of these sources of inaccuracy. The effect of each was studied in simulation and confirmed by experiment. These studies showed that in order to measure attenuation accurately, measurements must be made over a wide bandwidth with a phase-insensitive receiver large enough to capture the received signal when the beam is deflected by refraction.

Acousto-electric transducers, constructed in the Department of Physics, were used to provide these phase-insensitive receivers. The use of these transducers has clearly demonstrated the significance of phase-cancellation effects.

Quantitative imaging with ultrasound is also limited by the presence of anisotropic absorption and scatter. The appearance of a given tissue in a particular region depends on the direction in which sound propagates through it. Put succinctly, various tissues, muscle fibers in particular, appear differently in an ultrasonic image depending on whether they are viewed along or across their length. The tomographic system was used to quantify in detail anisotropic effects for liver, heart, and skeletal muscle. For example, a 2.2:1 change in the attenuation of dog myocardium was found, due not to an abnormality in the tissue but rather to a change in the direction of propagation of the sound through the tissue. Anisotropy of phase velocity and integrated backscatter have also been explored.

Although the studies of transmission tomography helped elucidate the problems in quantitative imaging with ultrasound and then served to verify solutions to those problems, this was of limited clinical value. In a tomographic procedure, ultrasonic beams must pass from an array of transmitters, through the body, to receivers, as both transmitters and receivers are rotated about the body. In such a procedure most of the ultrasonic radiation would be absorbed or reflected by the bones, lungs and air-spaces within the body so that very little of the original signal would be available for image formation. Therefore the approach was broadened to include imaging with reflected ultrasound. Here both the transmitter and the receiver of the sound reside in the same physical location and are moved over a small region of the body. To support this effort, a processing environment has been set up with a computer interfaced to the tomographic scanner, a digital echocardiograph designed and built at the BCL, and an array processor. With this equipment a start has been made on identifying the problems in quantitative imaging with reflected ultrasound using arrays of transducers and quantitative measurements with single-element transducers.

The diffraction-limited performance of linear phased arrays in pulse-echo mode were simulated to provide estimates of the size of tissue regions which could be characterized at locations throughout the field of view of the array.

Two dispersive tissue models were developed, which provide better estimates of attenuation than the traditional model which assumes phase velocity is constant. The density of elements needed in a two-dimensional transducer array of point-like elements was evaluated by scanning an excised, intact dog heart.

Several methods for processing the signals of the scans were devised or extended to meet the objectives of this project. A scheme for representing the sound field at the receiver in terms of its spatial moments has been proposed and tested. It was shown that quantitative imaging with a phased array requires combining element signals in a way that depends on the medium, a technique BCL called adaptive beamforming. Spectral filtering and generalized substitution techniques were applied to backscattered ultrasound to improve estimates of attenuation and to assess the computational burden in generating two-dimensional images of tissue properties. Also developed was a maximum likelihood estimator for attenuation measured with a transducer array.

One of the most important results of this work was that it was possible to demonstrate that a link exists not only between ultrasonic properties of tissue and its pathology, but also between ultrasonic properties and cardiac function. Information can be derived not only about the physical nature of cardiac tissue, but also about its physiologic function: is this region of the myocardium behaving normally? A cyclic variation in integrated backscatter from canine myocardium was found in which the maximum backscatter occurs near the end of diastole, and the minimum occurs near the end of systole. In the treatment of cardiac disease, a technique is emerging from this work which can quantify both the extent of damage to the tissue of the heart and the extent of loss of function.

5.3. Visualizing Chemical Processes

5.3.1. MMS-X

The National Collaborative Research Program (NCRP) was initiated as a component of the RR00396 grant to support the design and prototype development of a replicable, high performance graphics system. The NCRP program was the culmination of a series of design experiments which began in 1968 to explore a variety of hardware and software implementations of molecular modelling systems. The program was a response to an emerging need for molecular modelling systems capable of manipulating macromolecular (protein) structures. This need was identified as early as 1974 when a prototype system, the MMS-4 — built from macromodules, was shown to several groups of research chemists and crystallographers. There was sufficient interest for a plan to be formulated and presented to the NIH which called for CSL to design a high-performance, medium cost ($40,000) graphics system that could be replicated in small numbers. The approved plan allowed for the construction of a prototype system and the distribution of the production copies to selected research groups for the cost of components.

In 1977, with a working prototype of the MMS-X, the goals of the NCRP were expanded to establish and support a collaborating community of investigators working on the structural aspects of biologically important molecules, all equipped with common tools for molecular modelling and display. By the fall of 1979 the community consisted of ten research groups, eight of them outside St. Louis, each with their own MMS-X, and a team of engineers at CSL devoted to the development and support of the research groups. This was a unique situation in which a group of collaborators with diverse interests ranging from interpretation of crystallographic data on viruses to the investigation of the processes involved in the recognition of drugs by receptors, were united by the use of a common tool: high performance, interactive computer graphics.

The effects of this effort have been far reaching and profound. First, a selected group of high quality research teams has been provided access to an extremely powerful research tool whose cost would otherwise have been prohibitive. Second, the capabilities of the MMS-X were far superior to the those of then commercially available equipment. Third, the MMS-X was the forerunner of systems which have transformed the nature of research in the study of complex molecules. The architecture of the system, a small dedicated computer system whose primary function is graphical control, has been adopted by the newest and most advanced graphics systems from manufacturers such as those from Evans and Sutherland.

Another notable result of the NCRP was the development of a pool of common software shared freely among the users of the MMS-X system. As anyone who manages a computer system, or even a small research facility,

quickly learns, the primary cost of the system is not the initial equipment acquisition or even the equipment maintenance but rather the cost of software development. The group of collaborators, with identical equipment, produced an environment in which software could easily migrate from one site to another. This allowed groups with more software expertise to provide programs for groups with fewer personnel or less experience in software development.

The most significant result of the NCRP, and also the most difficult to quantify, was the increased productivity of the research groups which is directly attributable to the availability of the MMS-X as a research tool. The MMS-X allowed an entirely new way to visualize and manipulate models of large molecules. Because the researcher can manipulate the model of the molecule, rotate it in space, vary the magnification of the structure — manipulate the model in a myriad of ways, the MMS-X is several orders of magnitude more powerful than conventional modelling techniques.

The magnitude of this impact and the continued vigor of the community is indicated by the following data: of the approximately 45 high performance systems being used for molecular structure research worldwide, 25 are located in North America and 11 of these are MMS-X systems; the total time logged on the NCRP systems in the last two years exceeds 30,000 hours; of the 60 NCRP related publications cited in our annual reports from the past two years, over half represent reports of scientific progress in which the use of the MMS-X system made a significant contribution.

The usefulness of the MMS-X continues for those groups actively pursuing molecular research. The hardware and software techniques developed for the machine during the tenure of the NCRP continue to exert substantial influence on the designs of succeeding generations of molecular graphics software systems. Without the work of the NCRP and the community of scientists which developed these tools of molecular modelling, the pace of innovation in both the fields of systems development and molecular science would be much slower than it is today.

5.3.2. Mass Spectroscopy/Laboratory Biochemistry

Researchers from BCL became formally involved in computer instrumentation in laboratory biochemistry in 1969 and remained involved in this work until 1975, at which time the mass spectrometry program became a separate BRP resource. Several different applications were developed for the laboratory; all of them dramatically expanded the range of observable biochemical processes.

Initial projects included adapting a DEC PDP-12 for online data acquisition and control of a scanning mass spectrometer, and in devising a method for acquiring and analyzing data from a stopped-flow mixing system attached to a spectrophotometer which was used in studying enzyme kinetics.

The complete laboratory minicomputer with analog and digital I/O, mass storage and graphics terminal seemed to be adaptable to nearly every laboratory instrument and assay procedure. However, despite the decreasing costs, a great many of the applications encountered did not require the general power of a minicomputer system. This instrumentation project was begun just as 4- and 8-bit microprocessors were flowing into the commercial marketplace. After completing the first two projects, work was begun on using microprocessor systems for laboratory applications. Such systems would cost at most a few thousand (1972 dollars), far below the cost of a complete laboratory minicomputer. The first such device was built using the first commercially available microprocessor, an Intel 4004, at a component cost of under $400. It was initially used to monitor the output of a liquid chromatograph and later adapted to control the solvent-switching system of an amino-acid analyzer.

The simplicity and adaptability of the microprocessor-based controller encouraged the development of a laboratory microcomputer system which had greatly extended capabilities, but still cost significantly less than a minicomputer system. Two applications were selected for the initial design phase. The varied requirements of these projects ensured that the system would be general enough for use in further applications without component redesign. The engineering requirements of these applications fell between standard minicomputer instrumentation and special purpose system design; some special purpose hardware was built, but the replication of these components was straightforward and in general the larger problems of laboratory control were in software development.

The first application was the reinstrumentation of the amino-acid analyzer in the laboratory of Dr. Leonard Banaszak. The analyzer employed a fluorescent reagent which allowed the detection of amino acids at the picomolar level — a dramatic increase in sensitivity compared with conventional analyzers. The system controlled the timing and switching of the solvent valves, as the Intel 4004 did, and additionally added reagents at appropriate times in the interaction, monitoring leak conditions and collecting and storing fluorescence data. Data were displayed on a monitor and recorded by a small printer. The construction of this system allowed for the sequencing of proteins which were hitherto available in quantities too small for analysis.

The second application involved the automation of a split-beam scanning spectrophotometer in the laboratory of Dr. Craig Jackson. In order to study the activities of the compound prothrombin in blood coagulation, many time dependent adjustments must be made during the run. The microcomputer system allowed for automated data collection and for controlled manipulation of the device during the run.

The laboratory microcomputer system filled a need for low cost, adaptable on-line computing not then met by the computer industry. The applications themselves have considerable scientific merit, contributing as they do to the

extension of important biological techniques. Due to its sensitivity to extremely small quantities of substance, the amino-acid analyzer allowed a much larger class of proteins to be sequenced. The scanning spectrophotometer, in conjunction with an ultracentrifuge, has been used to study several components of the mechanisms of blood coagulation.

5.4. Development of Research and Clinical Tools

5.4.1. Radiation Treatment Planning

In the United States, about half of all cancer patients are treated with ionizing radiation during the courses of their diseases. The goal of radiation therapy is to control the malignant disease by delivering a radiation dose to the tumor volume which is sufficient to kill tumor cells while at the same time minimizing the amount of radiation damage to surrounding normal tissues.

Treatment planning in radiotherapy is a procedure for selecting and placing sources of ionized radiation so that their combined effect yields an optimal spatial distribution of absorbed dose in a particular region of the body. Radiation Treatment Planning (RTP) was one of the first major projects pursued by the Biomedical Computer Laboratory. After five years of effort, a complete system of hardware and software was transferred to the commercial arena following critical evaluation at six major radiation-therapy centers in the U.S. and Canada. This transfer took place in 1970 with Artronix Inc. assuming responsibility for continued development and support. Today there are approximately 150 such systems installed worldwide. In addition to the Artronix installations, other manufacturers offer functionally similar systems styled after the original development at BCL. Systems developed later on the PDP-8 by Dr. Roy Bentley of the Royal Marsden Hospital in England, and on the PDP-11 by Dr. Jack Cunningham of the Ontario Cancer Institute, are of interest since both men were key contributors to the BCL development.

These systems are generally judged to be successful in automating what was previously a laborious manual operation, although significant deficiencies continue to detract from their efficacy. These stem from the dependence of the computational algorithms on inadequate mathematical models of the underlying physical processes characterizing the interaction of ionizing radiation with matter at the atomic level. For this reason the presently available methods of absorbed dose calculation are approximate, thus limiting their real utility in radiation treatment planning. BCL, like several other groups, recognized for a number of years that computed tomography (CT) could provide a remedy for the shortcomings of the present methods of absorbed-dose calculation. Accordingly in 1977, development was begun of a new approach to absorbed dose prediction, based on fundamental physical principles and taking advantage of the information provided by CT scanning.

The general objectives of the renewed effort have been to develop algorithms for computing three-dimensional dose distributions within inhomogeneous tissue regions valid for radiation fields of arbitrary shape and size, and to apply advanced computer technology in the implementation of these algorithms to render them clinically useful. A specific objective of the initial work was to investigate the validity of the physical basis of the mathematical model on which the methods depend. For this purpose, theoretical values of absorbed dose computed by the BCL method were compared with some published experimental results. This phase of the work has been largely completed, computed absorbed doses having been obtained which were in excellent agreement with values obtained by measurements in phantoms. With the physical validity of the method thus established, attention has shifted to the second of the original objectives: to render the method useful in a clinical setting. For this purpose fast special-purpose digital hardware (VLSI) is being designed that will perform the computations quickly enough for them to be helpful to the therapist, and that will allow the development of clinically useful three dimensional simultaneous displays of computed dose distributions superimposed on the corresponding CT-scan images.

5.4.2. Broadcast Information Systems

In 1968, a broadcast information system concept was proposed by W. A. Clark and C. E. Molnar as an approach to distributed computing and information processing. The central idea is the use of a one-way, wide-bandwidth communication system to provide programs and data to distributed processors. In its simplest form, such a system would contain a fixed library of information stored at a central node, called the transmitter, and an arbitrary number of distributed processors, called receivers. The transmitter continuously broadcasts the contents of the library over a high-bandwidth transmission network. The distributed processors (receivers), obtain programs and data by waiting until the desired information appears in the broadcast stream and copying it into their own local memory. In this way, an unlimited number of receivers can be sustained by the same broadcast source, since the operation of the transmitter and transmission network are entirely autonomous from the operation of any of the receivers. The transmitter and communication network function as a virtual mass memory for the receivers.

An experimental implementation of such a system, using cable television equipment and signal conventions derived from the NTSC color-television standard was constructed under University support, and formed the basis for a subsequently granted patent. In May, 1974, support was obtained from the National Center for Health Services Research and Development for the further development of this concept and its application to the collection of patient-history in the University's department of Psychiatry. Using the Beth Israel Converse system developed by Slack and Bleich as a functional model, a

prototype broadcast system with four receivers was developed and used to administer psychiatric interviews. Programs originally developed for the Beth Israel system were also translated into the appropriate broadcast format.

Working with members of the Department of Psychiatry, the CSL staff translated the NIMH Diagnostic Interview Schedule (DIS) for use on the broadcast system. This particular interview was an ideal candidate for such a translation, as the following will make clear. The DIS was heretofore administered as a paper and pencil interview by trained personnel. The interview is difficult to administer since there is much branching to different sections of the interview depending on previous responses. The *paper and pencil* interview process is as follows:

(1) Conduct the interview.

(2) Encode the responses on punched cards.

(3) Clean the data; check the responses with a computer program to make sure that proper branching occurred during the interview. If there were branching errors, the data would be corrected as much as possible.

(4) Run the data through a computer program to generate a diagnosis for the patient.

The broadcast version of the interview eliminated the need for steps two through four and aided in step one. Since the data are collected on a computer-based system, the data are already in a machine-readable form, eliminating the need for step two. The system itself eliminated the need for the interviewer to keep track of the branching within the interview itself — such branching is done automatically. Lastly, a portion of the broadcast stream contains a program which can perform the diagnosis immediately on completion of the interview. The turnaround time from administration of the interview to generated diagnosis has been reduced from 24 hours to 2 hours.

After the completion of the DIS project, in 1977, activity with the broadcast technology slowed down. In late 1982, a search for new funding for further development of broadcast techniques and applications was begun. This effort has included licensing of the original broadcast patent through the Research Corporation of America and new collaborations within the medical school, notably with the Department of Internal Medicine. A project just now beginning will study the automation of insulin dosage algorithms for diabetic patients with the end goal of making intensive insulin therapy available to a large portion of the diabetic population. Further development of the broadcast system will be a significant activity for the new Institute for Biomedical Computing.

The initial broadcast system design proved to be effective for supporting rapid and comfortable man-machine interactions. Using a single television channel as the broadcast medium, with a transmission rate of about three million bits per second, an interactive questionnaire with large amounts of

branching in the selection of subsequent questions can be presented to an unlimited number of users with a system response time of under one tenth of a second for a library containing a half million characters. With the use of multiple television channels over the same cable, the library size can be greatly extended without sacrificing the response time of the system. With the development of the cable-tv industry, a transmission network is being built that makes the the broadcast technology an important possibility for the inexpensive distribution of computer power to the home.

The particular features of the broadcast approach that make it attractive are the rapid response time that can be achieved with proper design, the appropriateness of the method in the light of the rapidly declining costs of processor and memory hardware in comparison with the cost of mass storage devices needed to support the operation of distributed computers and the advantages of maintaining and updating a single library of programs rather than a large number of copies. Broadcast techniques hold great promise for being able to deal with these complex display problems while maintaining system response time.

5.4.3. Speech and Hearing

The Speech and Hearing Group was established in 1967 to address technical problems related to basic research in speech and hearing. Members of this group included staff of Central Institute for the Deaf (CID) and BCL. The underlying interest throughout this work has been to understand the problems of hearing impairment by developing research tools for the study of speech and hearing and to develop aids for the hearing impaired.

The first project undertaken was the development of an instrument for the recording and playback of speech sounds (dubbed RAP for Random Access Programmer). The instrument utilizes digital methods for storage of sounds in digitized form on cartridge discs. Once recorded, the sounds can be randomly accessed and played back. For the psychoacoustitian, digital recording and playback amounted to a revolution in the nature of his experimental method. As an example consider the methods, before and after RAP, of testing a person for speech perception. The basic method in testing for speech perception is to present the subject with a random set of words and judge the ability of the subject to correctly identify the words, based upon multiple presentations of each one. Before the advent of RAP a tape recording containing a pseudorandom arrangement of the set of words would be played for the subject. The order of events in the tape was rigid and if the test had to be administered to the same subject on several occasions, the results could be contaminated by the effects of memorizing the given tape. The time required to prepare new tapes, different orderings of the same stimuli, was great. After RAP was introduced into the laboratory the same set of speech sounds could be presented

in endlessly different orderings, or even, when used in conjunction with a small laboratory computer, the order of presentation of the stimuli could be based on the history of subject response.

The first RAP unit was *hardwired* and contained operator controls similar in function to an audio tape recorder. Following this basic design several programmable systems were subsequently assembled at CID and continue to be used in psychophysical studies involving hearing-impaired and normal-hearing adults and children and in comparative studies of noise and speech perception with chinchillas.

To support these basic laboratory systems, a small minicomputer was assembled with peripherals including a graphics display, graphics tablet, analog-to-digital and digital-to-analog converters for applications of speech analysis and speech synthesis. The disc formatting of the various devices was such that speech data could be exchanged with the various computer systems in the laboratory. It was used for a variety of tasks.

A synthesizer program was written for this system to duplicate the hardware speech synthesizer used in speech experiments at the Haskins Laboratory at Yale. In this way, *Haskins-like* stimuli were generated at CID and used in speech perception studies with chinchillas to study categorical perception in non-human subjects. The general findings from these experiments suggests that categorical perception can be demonstrated with non-human subjects for certain speech-like sounds. This also suggests that the perception and categorization of sounds, is not a unique function peculiar to the speech processing portion of the human brain, but is instead a general property of mammalian auditory processing.

The system was also used to develop an improved speech perception testing algorithm (called MEGS). Conventional methods of speech testing have used randomized word lists in which test words are presented to the subject with equal frequency. The MEGS test, on the other hand, presents the difficult sounds more frequently by setting aside sounds that are correctly identified. Since the sounds are stored in digital form on a cartridge disc, selection of the sound to be presented can be contingent on the patient's response. This is in contrast with current clinical speech testing that uses magnetic tapes with word sequences in a pseudorandom but fixed order. The sounds that remain in an active pool at the end of a MEGS test are those that have been misidentified or confused by the patient. The long-term goal of this work has been to analyze the sounds that remain at the end of the test and to determine common spectral and other signal properties that are related to specific hearing impairments.

The system also serves as a speech analysis tool for various studies related to communication problems of the hearing impaired. The work to be noted here involves:

(1) the development of a model of the acoustic transmission properties of the throat wall to determine the acoustic transmission properties of the glottus;

(2) the study of glottal source functions for male, female and child subjects with normal and pathological voice quality;

(3) studies involving lip reading displays;

(4) studies of electroacoustic stimulation as an alternative input for the hearing impaired;

(5) basic studies of speech perception including computer modelling of the cochlear transduction process and vowel normalization studies;

(6) a comprehensive interactive speech analysis program called *speech microscope*, enabling the user to record, edit, and playback speech sounds and to perform a variety of analyses on these sounds.

The BCL-CID collaboration has provided tools for the study of speech and hearing related to the problems of the handicapped. It has provided a foundation for the use of digital methods in meeting the needs of the hearing handicapped. Although the collaboration has concluded, work is continuing at CID under separate funding utilizing advanced computer techniques in the modelling of speech perception and, more recently, in the development of a digital hearing aid that incorporates new computer-based clinical fitting procedures.

5.4.4. Information Systems

The formation of the Information Systems Group (ISG) in 1975 was an effort to bring the study of database systems and machines under one roof. Database machine design brings together problems in hardware design, software design and human factors. Whether retrieving results from the clinical laboratory computer or making a statistical query of patient survival in a neonatology database, people use databases to answer questions. Designers of database systems must take into account a wide variety of imprecisely formulated queries, changes in the conception of data, and the need for rapid searches of vast amounts of information. These problems are not unique to medical research — there is substantial activity in database design throughout the computer industry — but the problems are amplified by the rapid rate of growth and change in medical knowledge.

There have been a succession of models of data relationships, some of which have served as adequate representations of, for example, a business database. But none of these models have had the generality necessary to deal with the complex medical relationships: problems, complications, diagnostic procedures, therapies, medications, all of these intertwined and existing over periods of years for any single patient.

The work of the ISG began with developing a data model. called the Abstract Database System (ADS), which served to guide subsequent work in architecture, hardware, and trial implementations. ADS has been used to describe these relationships in a concise and understandable way. The model incorporates and integrates the major data models and concepts of the past decade. ADS unifies several modern data models and provides a powerful method for translating from one data model to another. Furthermore, several of the major concepts of ADS can be implemented in VLSI hardware (e.g., pattern matching). Since these pattern manipulation operations are good candidates for VLSI implementation, there would be a direct connection between the conceptual data model and the custom microelectronic implementation.

After the completion of a software implementation of ADS it was used to specify and construct a subset of a neonatology database. A program for translating several popular query-languages (SQL and QUEL) into ADS was also implemented. The former demonstrates the capability of ADS to naturally represent complex medical information. The latter points to ADS's capability as a general model capable of translating between other data models.

The prospect of ADS pattern matching operations implemented in hardware offers the potential of data searches that would be faster than any software encoded procedure. In the area of hardware, a custom design for an experimental pattern matching memory module was developed. Chips were fabricated and tests performed on them to study problems of concurrency, capacity and cost.

Associative memory is a widely used term to describe any sort of memory which retrieves information through the contents of a memory location instead of its address. The pattern matching memory designed by the ISG is a powerful form of associative memory. In a conventional memory system each location has a specific address. Most searching procedures are address dependent; they depend on examining the contents of each address, one at a time. In the associative memory, information can be accessed by specifying the pattern that the memory must match. As a result, the searching operation becomes much more powerful because the entire memory can be searched with one command.

Associative memories, particularly pattern matching memories, have heretofore been prohibitively expensive but the evolution of tools for custom designed VLSI circuits can make their application cost effective.

6. Summary of Research Impact

Each of the aforementioned projects, in its own way, has had substantial impact on the national biomedical community. The LINC set the pattern of a generation of minicomputer applications in medicine. Macromodules have influenced the thinking of forward-looking computer scientists who recognize the importance of the speed-independent, delay-insensitive discipline for computer system design. Molecular graphics has gained acceptance through the development and fielding of MMS-X and is now an important tool in the molecular modeling and x-ray crystallographic communities. Studies of feline cochlea have reversed the conventional wisdom that the auditory system is linear and have awakened many auditory physiologists' interest in nonlinear phenomena. Work in radiation treatment planning has led to the fielding of over 200 systems in radiation therapy centers throughout the world. Work in ECG rhythm analysis resulted in algorithms that were duplicated or emulated in systems marketed internationally by the Mennen Medical and Hewlett Packard Corporations, as well as strongly influencing a generation of commercial systems. The algorithms, functional capabilities and system architecture developed in the surgical intensive care unit have been shared with many others and the system has been emulated by Midwest Analog and Digital Inc. Positron emission tomography has become an important tool for non-invasive studies of biochemical and pathophysiologic phenomena in the heart and brain. All three U.S. manufacturers of PET instruments have used algorithms developed at the Laboratories in their tomographic products. Computer controlled mass-spectrometry has improved the detection of substances in biological material by an order of magnitude or more, opening new vistas for research in many fields. MUMPS in the minicomputer environment has been standardized, has been propagated widely and is in heavy use throughout the medical community. Finally, the major new initiative at CSL to explore the role of the macromodule concept in the design of VLSI circuits and to assimilate VLSI technology into the Washington University community promises to yield important results in developing new computer systems.

7. Acronyms and Abbreviations

The text of this summary and some of the titles in the bibliography use acronyms and abbreviations from a variety of sources. To help the reader, they have been collected together in this section in alphabetical order.

ADS	Abstract Database System (Data model developed by ISG for database research.)
ARGUS	Arrhythmia GUard System (Set of algorithms for analyzing single-lead ECG recordings for arrhythmias.)
ARGUS/H	ARGUS High-speed (Analysis system for long-term single-lead ECGs at 60 times real time.)
ARGUS/2H	ARGUS 2-lead, High-speed (ARGUS/H for two leads.)
BCL	Biomedical Computer Laboratory
CAT	Computer-Aided Tomography (see CT below)
CID	Central Institute for the Deaf
CRT	Cathode Ray Tube (Oscilloscope screen. Shows an image made up of small dots of light. Used as display for most computers today.)
CSL	Computer Systems Laboratory
CT	Computed Tomography (A more recent acronym replacing CAT.)
DEC	Digital Equipment Corporation
DIS	Diagnostic Interview Schedule (Complex interview schedule from NIMH used as a test for the Washington University broadcast system.)
ECG	Electrocardiogram (Representation of the electrical activity of the heart.)
EMI	Electrical and Musical Industries, Ltd. (A British corporation that was the first to manufacture CT scanners. Now known as just EMI.)
FFT	Fast Fourier Transform (A method of analyzing signals.)
HAVOC	Histogram Average Ogive Calculator (Digital averaged-response computer for audiometry research designed at CID.)
ISG	Information Systems Group (Group set up in 1975 for the study of database systems and machines.)
Kb	Kilobyte or 1024 (2 to the power 10) computer bytes where a byte is eight binary bits. Usual measure of capacity of computer memory or of disk space.

Kword	Kiloword or 1024 (2 to the power 10) computer words. Often used as a measure of the capacity of machine memory or disk space. Nowadays Kb (q.v.) is more usual.
LINC	Laboratory INstrument Computer (Early minicomputer. Designed in Cambridge 1961 to 1963, later built by DEC. CSL was responsible for the LINC Evaluation Program and many enhancements to the LINC.)
LINC-8	LINC and PDP-8 (DEC minicomputer, operated as either LINC or PDP-8.)
MCF	Medical Computing Facility
MEGS	Miller, Engebretson, Garfield and Scott method (Speech perception testing algorithm developed at CID.)
MMS-X	Molecular Modelling System (Graphics display system for modelling molecular structures. The X stands for either experimental or exportable, depending on the user's preference.)
MUMPS	Massachusetts General Hospital Utility Multiprogramming System. (A computer language/operating system designed at MGH by Octo Barnett for building and manipulating medical databases.)
NCRP	National Collaborative Research Program
NIH	National Institutes of Health
NIMH	National Institutes of Mental Health
NTSC	National Television Standards Committee (Designation of the U.S. standard for color television.)
PC	Programmed Console (WUCL designed computer.)
PC-1200	PC Model 1200 (Minicomputer manufactured by Artronix, St. Louis.)
PDP	Programmed Data Processor (Abbreviation for DEC minicomputers. The PDP-4, PDP-5, PDP-8 and PDP-12 were influenced by design of LINC.)
PET	Positron Emission Tomography (Technique for producing three-dimensional reconstructions of internal organs using short-lived artificial radio-isotopes such that the reconstructions showed aspects of the patient's metabolism. The algorithms and computer architecture were largely developed at BCL.)
PVC	Premature Ventricular Contraction. (Type of ventricular arrhythmia, detection of which is one of the primary goals of long-term ECG analysis programs.)

QRS	The most prominent feature of an electrocardiogram, designated by the names of its constituent waves (others are P, T).
QUEL	Query Language (A language used to formulate requests for retrieving data from a database.)
RAP	Random Access Programmer (BCL-designed system for controlling recording and playback of speech sounds.)
SDAG	Systems Design Aid Group
SQL	Structured Query Language (A popular query language, used to formulate requests for retrieving data from a database.)
TRIMOSBUS	TRIple Metal-Oxide-Semiconductor Bus
UCLA	University of California at Los Angeles
VAX	Virtual Architecture Extension (Acronym for a class of minicomputers made by DEC.)
VLSI	Very Large Scale Integration (A technology concerned with fabricating millions of logic elements on a single silicon wafer.)
WU	Washington University
WUCL	Washington University Computer Laboratories

8. Classified Index to the Bibliography

The above essay contains a descriptive narrative of the technical developments at the laboratories. However, this is of limited use as a key to the mass of literature which was generated under RR00396.

This chapter therefore contains two indexes to the 1300 citation bibliography which follows. The first is by medical specialty, the second by technology. Citations are multiply indexed where appropriate. Sadly, all the references are listed without annotation.

In the case of the index by medical specialty, there are references under each of the main headings which are primarily medical studies which use a particular technology, such as nuclear medicine, as a vehicle for the study. The index includes such secondary keys only for those technologies in which BCL or CSL has made a significant contribution to the field. For example, in the broad category of biochemistry/chemistry/pharmacology there are many studies in the field of crystallography by scientists who were funded under RR00396. Since neither of the two laboratories contributed engineering skills which directly advanced the field of crystallography, these studies are listed in the *unclassified* section.

The index by technology consists almost exclusively of engineering references.

8.1. Index By Medical Specialty

8.1.1. Cardiology

Electrocardiography

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