Evolution of the Center for Computational Biology (CCB)
A Historical Account

The Early Years: 1964 – 1984

The Founding of Biomedical Computer Laboratory (BCL) and Computer Systems Laboratory (CSL)

The vision of the CCB (Center for Computational Biology) began long before the IBC (Institute for Biomedical Computing) and the CMD (Center for Molecular Design) existed. It even began before the CSL (Computer Systems Laboratory) was given birth. The vision was a seed that began to grow somewhere in the Spring of 1964, when Jerome R. Cox, Jr. had persuaded the School of Medicine to charter BCL (Biomedical Computer Laboratory) as a Research Division to develop and apply computer technology to biomedical research problems. His interest in this area had developed from work he and his students had done at the Central Institute for the Deaf on laboratory computers for collecting and analyzing data from auditory experiments. At the same time, a group at the Massachusetts Institute of Technology, led by William N. Papian, Wesley A. Clark, and Charles E. Molnar, which had developed the Laboratory Instrument Computer (LINC) as a tool for biomedical computing, was looking for a new home. With the encouragement of Dr. Cox and the assistance of Provost George Pake of Washington University, the MIT group relocated to St. Louis and formed the Computer Research Laboratory (CRL), a unit that reported administratively to the Provost's office. (CSL would later be formed from CRL.)

Early Program Goals and Activities

Cox and Clark had arrived independently at the conclusion that it was important to place computing tools directly in the hands of researchers rather than to centralize the machines and the skills needed to use them. This theme was pursued jointly by the two laboratories through the support of LINC users at Washington University, and through a National LINC Evaluation Program operated by CSL. By the end of the decade, a national community of LINC users had been established and supported through the construction of additional LINCs, the design of improvements to LINC hardware, and the development of new interfaces, utility programs, and application software. A LINC users group provided documentation, program exchange, and consultation on problems of common interest.

The LINC program and other activities of the two laboratories received generous support from the Division of Research Resources of the National Institutes of Health. Coordination was managed through a loose confederation called the Washington University Computer Laboratories (WUCL), chaired by Dr. Cox. While sharing broad overall goals and collaborating in many areas, the programs of the two laboratories acquired different emphases.

Biomedical Computer Laboratory (BCL) Program Development

The BCL program undertook as its major goal the development of new application areas suitable for laboratory computing. Examples of early work include projects in sensory evoked-response recording and analysis, radiation treatment planning, nuclear medicine, electrocardiographic (ECG) rhythm monitoring in the coronary-care unit, fetal ECG analysis, instrumentation and software for monitoring patients in intensive-care units, computer-based acquisition and analysis of physiologic data in the cardiac-catheterization laboratory, analysis of CAT-scan data, and quantitative tissue characterization via ultrasound. Typically, these projects involved collection of experimental data, use of mathematical models and analyses, and close interaction between the scientist-user and the computer system. Close collaboration of biomedically trained researchers with technically trained members of the BCL staff and its colleagues in the School of Engineering proved to be a very productive means of finding effective solutions to biomedical computing problems.

This style continued through the change of leadership of BCL occasioned by the move of Dr. Cox to the Chairmanship of Computer Science in 1975, and his succession as BCL Director by Lewis J. Thomas, Jr. The theme of the BCL program, quantitative biomedical imaging was defined by a collection of application projects for which research in quantitative biomedical imaging was needed. Projects of BCL and its collaborators were in positron-emission tomography (PET), physical and RFLP mapping of DNA, electron-microscopic autoradiography, various aspects of ischemic heart disease, computational optical sectioning, radiation treatment planning, and applications of massively parallel computation to computationally demanding algorithms. Mathematical and computational methods for the optimal estimation of biomedical images obtained through various imaging modalities played a major role in many of these projects.

To support these projects, BCL Associate Director G. James Blaine led the development of new computing and networking tools for image presentation, analysis and quantification (IPAQ), which resulted in multiple computing and display resources at BCL, and a network interconnecting them with laboratories of research collaborators. BCL also participated in the development of the Biomedical Network portion of a campus-wide computer-communications network, under the leadership of Dr. Cox.

Development of the Computer Science Laboratory (CSL)

The Computer Research Laboratory was soon reorganized as the Computer Systems Laboratory, under the leadership of Wesley A. Clark, and the Computer Components Laboratory, headed by William N. Papian, that moved to the School of Engineering. With initial support from NIH, augmented by major support from the Advanced Research Projects Agency of the Department of Defense (DARPA) from 1967 to 1974, the development of Macromodules as tools for designing and building experimental computer systems became the dominant CSL project. The core group that had moved from MIT was greatly augmented by new staff, faculty collaborators from the School of Engineering, and students, who worked intensely until an inventory of nearly 1,000 Macromodules was completed in 1973. At that time, Charles E. Molnar succeeded Wesley Clark as the Director of CSL, and emphasis in the CSL program shifted toward applications experiments such as a series of machines (MMS-1 through MMS-4) for molecular graphics and drug design. This work, carried out with Macromodules, led to a system (MMS-X) that provided very rapid and responsive manipulation of calligraphic models of molecules by a user, with sufficient speed and resolution to support the fitting of X-ray maps of the electron density of protein molecules by these models. Numerous copies of this hardware/software were distributed by NIH to leading crystallographic labs nationwide. The MMS-X could also use its specialized display hardware to perform coordinate computations orders of magnitude faster than could be done by its host minicomputer. The MMS-X activities also stimulated the development at Washington University of research in molecular modeling applied to drug design led by Garland R. Marshall. The specialized software/hardware developed were spun out by Washington University to form the nucleus of Tripos, Inc. (TRPS, Nasdac) in 1979, leader in computer-aided drug design software for the pharmaceutical industry.

Perhaps the most significant technological research accomplishment by CSL was provided by studies of the 'glitch' or metastability problem that arises in communication with computer systems. The problem was noticed during the LINC work at MIT, by the first published oscilloscope photos showing the problem, and the first theoretical study that demonstrated the universality of the problem, were done at CSL. For a number of years it was difficult to convince many workers in the computing field of the importance of the problem, but as high-speed multiprocessor systems have evolved, the metastability problem has been accepted as one of the fundamental limits to computing speed and reliability. CSL's unique skills in testing circuits subject to this problem, and in designing safer circuits and system approaches, have been increasingly sought by industry.

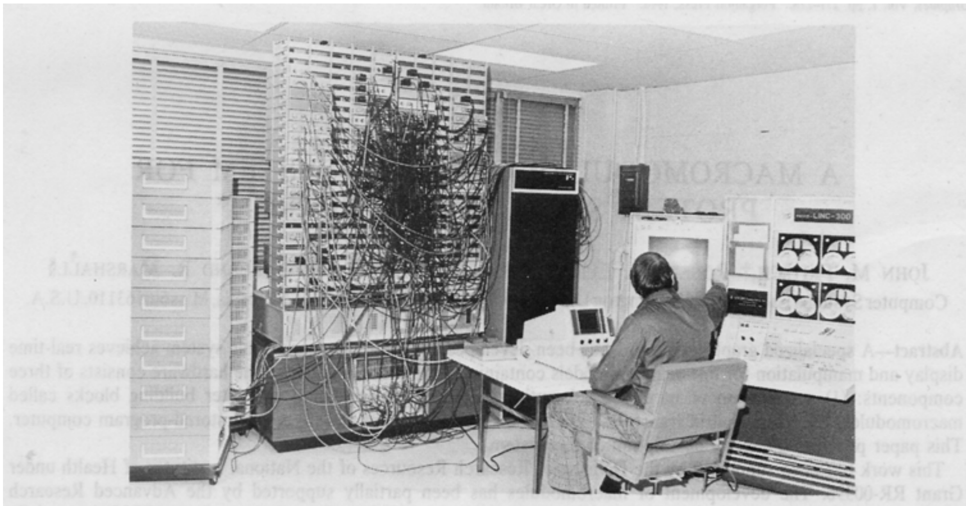

Fig. 1. Current version of the Macromolecular Modelling System. The components, from left to right, are (a) auxiliary memories (4K of 12-bit words to each box within the stacks, except for the lower two boxes which are a power supply and a controller), (b) macromodular processor, (c) (below) LINC-to-macromodule interface, (d) Evans and Sutherland LDS-1 Matrix Multiplier, (e) (foreground) LINC scope and keyboard, (f) Evans and Sutherland LDS-1 Line Drawing Scope and (g) micro-LINC 300.

CSL's further work on Macromodules was directed toward reducing their cost and developing new methods for the design of the kinds of circuits that they required. This work was overtaken by the rapid development of very-large-scale integrated circuits (VLSI), and the majority of work in CSL quickly became focused on acquiring the skills and tools needed to design VLSI integrated circuits. Related work encouraged and contributed to the development of formal mathematical theories used as a reliable means for specifying and designing computer systems employing distributed asynchronous control. These tools and methods were then applied to the development of a family of Image Manipulating Modules (IMM) capable of storing, manipulating, and displaying large multi-dimensional images.

A major final report to DARPA on their phase of support of the Macromodule project, delivered in 1974, comprised 14 volumes. Other CSL activities were documented through informal internal memoranda, and publications in the open literature.

Both laboratories have played a major national role in pioneering the acceptance of laboratory computing by the biomedical research community. The common elements of the many successful projects of this kind were the close involvement of scientific collaborators throughout all stages of system design, development, and evaluation, as well as the natural introduction of students from the engineering disciplines into the biomedical research laboratory. The two computer laboratories not only drew from the strengths of Washington University, but also contributed people to important leadership roles in the University. Most notable among these were Thomas T. Sandel, who became Chairman of Psychology, Russell R. Pfeiffer and Donald L. Snyder, who became successive Chairman of Electrical Engineering, Jerome R. Cox, Jr., who became Chairman of Computer Science, and Edward L. MacCordy, who became Assistant Vice-Chancellor for Research.

The Institute for Biomedical Computing: 1984 – 2000

Institute for Biomedical Computing (IBC)

Various forces acting both from within and outside of the University led to the succession of WUCL by a new organization. The Institute for Biomedical Computing was established on July 1, 1984, as a new organizational unit that encompassed BCL and CSL and established a formal connection to both the Schools of Medicine and Engineering. As you will recall, the primary focus of these two laboratories was to explore special purpose computing (CSL) and to provide hardware and software (BCL) support to a variety of computer-based initiatives at Washington University Medical School. As access to personal computers that could be readily adapted to laboratory applications became commonplace, the need for specialized hardware design diminished and the two laboratories were merged in 1984 as the Institute for Biomedical Computing. While the primary mission of the Institute for Biomedical Computing was to pursue research in the use of advanced computational and theoretical methods for the solution of biomedical problems, the vigorous pursuit of those problems sometimes uncovered fundamental issues in the methodology of computing that became research subjects in their own right.

The reorganization provided a new academic status that permitted primary faculty appointments in IBC. Drs. Molnar and Thomas became the Director and Associate Director of IBC, while retaining their roles as Directors of the CSL and BCL components. The organization of additional IBC components, such as a Medical Informatics Group under the direction of Mark E. Frisse, and a Center for Molecular Design under the direction of Garland R. Marshall followed closely on the heels of IBC's restructuring.

Prof. David States, Department of Genetics, became the new Director in 1992, where he remained until the IBC was dissolved on June 30, 2000.

The Center for Molecular Design (CMD)

CMD was established at Washington University in 1988 to accelerate the impact of scientific advances in computational chemistry on practical problems by focusing resources on current limitations to effective applications of molecular modeling. It was the culmination of over twenty-five years of research in molecular modeling and computer graphics at Washington University. It was headed up by Prof. Garland Marshall as a component of the Institute for Biomedical Computing. He began in the late 1960's in collaboration with CSL to utilize the primitive computers (LINC, PDP12) available for molecular graphics and conformational analysis. A unique element in the approaches taken here, historically, has been an emphasis on systematic evaluation of solutions to complicated molecular systems and practical applications to medicinal chemistry. This led to the development of an integrated modeling package which was the precursor of SYBYL, the software package marketed by Tripos Inc., a leader in the field. The set of algorithms developed collaboratively with Prof. Richard Dammkoehler and his colleagues of the Department of Computer Science for systematic search of conformational space have set the standard for systematic conformational analysis (dead-end elimination). A major emphasis at CMD was the development of effective tools for molecular design and the training of scientists in the applications of computational chemistry to therapeutic problems. Thus, Washington University has trained many of the leaders of molecular modeling groups in the pharmaceutical industry and in academia. Prof. Marshall has received various awards in recognition of his contributions to computer-aided drug design during his directorship of the Center for Molecular Design.

The Center for Computational Biology: 2000 – Present

The Center for Computational Biology (CCB)

Administratively, CMD was a division of the Institute for Biomedical Computing (IBC), under the joint responsibility of the Deans of the Schools of Engineering and Medicine. In 2000, after due deliberation, IBC was reorganized to include tenured faculty in three departments (Biochemistry and Molecular Biophysics, Biomedical Engineering, and Genetics) as the Center for Computational Biology, to focus on the unique opportunities presented by sequencing of the human genome as well as the genomes of other species, including pathogens. The presence at Washington University of the Genome Center, that has had such a prominent role in sequencing the human genome, has provided a rich environment for genomics and bioinformatics (Profs. Brent, Eddy, Gish, States and Stormo).

Raison d'être

Common intellectual ground that cuts across departmental disciplines:

- Molecular modeling and statistical mechanics
- Genome analysis and comparative genomics
- Statistics and probability
- Databases
- Algorithms
- Shared infrastructure
- High performance computing and networks
- Database infrastructure (molecular sequence, structure, motifs, and expression)
- Dissemination to the scientific community through web based servers/resources
- Common space for seminars, classes, reading and interaction

In 2001, a series of renovations began in the CCB, to house the new faculty they were recruiting to complement and expand current strengths in computational biology. In the course of two years time, the entire building (formally called the Old Shriners Hospital complex) at 700 S. Euclid was overhauled and renovated, providing the facility with new state-of-the-art computer equipment with a brand new teaching lab. Currently, CCB houses five academic faculty (three with primary appointments in Biochemistry and Molecular Biology and two with primary appointments in Biomedical Engineering). Other associated CCB faculty, from those departments as well as Genetics, are housed elsewhere due to wet lab requirements.

Equipped with new facilities and new faculty, the CCB continues to build on its international reputation in computational chemistry, drug design and bioinformatics by development of useful approaches in molecular design and application of computational biology to practical problems. New faculty with complementary expertise in computational biology are being recruited to CCB. In addition, internationally recognized computational chemistry software has resulted from the work of faculty and staff. These include the widely distributed TINKER package developed by the Jay Ponder group (distributed freely over the web, http://dasher.wustl.edu/tinker/) the RACHEL™ package written by Dr. Chris Ho (Marshall group) and distributed by Tripos, Inc. and Prof. Nathan Baker's APBS program (Adaptive Poisson-Boltzmann Solver), which is also distributed freely over the web (http://agave.wustl.edu/apbs/).