**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**NATIONAL INSTITUTES OF HEALTH**

**NATIONAL CENTER FOR RESEARCH RESOURCES**
**BIOMEDICAL TECHNOLOGY AREA**

# ANNUAL PROGRESS REPORT (8/1/03 – 7/31/04)

1. PHS GRANT NUMBER: P41RR05969
2. NAME OF RECIPIENT INSTITUTION: Macromolecular Modeling and Bioinformatics
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4. REPORTING PERIOD:
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   B. TO (Month, Day, Year): July 31, 2004
5. PRINCIPAL INVESTIGATOR:
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10. URL: `http://www.ks.uiuc.edu`
11. Was Patent or Copyright awarded this grant year: N
12. Total % effort related to AIDS research: 0%

Grant Number: P41RR05969
Report PD: (8/1/03 – 7/31/04)

# Contents

## Introduction

Living systems are made of molecules which form the bedrock of life, from the simplest to the highest form. The molecular level is woven into an awesome fabric of higher and higher levels of organization, but the molecular basis persists, best documented by how we battle most diseases, namely with drugs, i.e., molecules. Of course, the appreciation of the role of molecules in living systems has been shared by many researchers for a long time. New today is the wealth of detailed information on the molecular architecture of living cells that has become available, not only through knowledge of sequences, but also of structures. Furthermore, we understand much better how single molecules, e.g., proteins, assemble into larger functional units, how these units partake in networks of other units, and in what type of environment they exist in cells. In regard to the latter, it has been stated that 70% of drugs act on membrane proteins in human cells. Much of this knowledge implies a steep price since the molecular machines of the cell are huge at the scale of conventional chemistry. While a chemist can envision easily the molecules in a test tube, build a model of them, and perceive their dynamics, a biologist is overwhelmed from the outset: key machines of the cell consist of thousands to millions of atoms. The only chance to master intellectually the relevant molecular processes of cells is through computer graphics and computer modeling.

The software tools of structural biology are primarily molecular graphics and simulation programs. Even though there exist many programs to analyze macromolecular functions, the software is suitable mainly for experts. However, with a strong investment of effort, one can develop software for macromolecules that can be used intuitively and productively by biomedical researchers. This opportunity defines the mission of our NIH Resource. The success of our existing software, VMD, NAMD, and BioCoRE, hinges on a continuous partnership between a group of computational biologists engaged in biomedically relevant research projects and a group of computational scientists developing the necessary software tools. The two groups have shared common laboratory space for fifteen years, and have grown into a closely knit team through continuous interaction.

But our Resource has always measured its main impact by the quality of our collaborations with leading experimental groups. We receive many requests for collaborations and select projects on the basis of their quality and biomedical relevance. These criteria were applied to the selection of past collaborations that often led to joint, in many cases highly cited, publications which cover an impressive variety of biomolecular systems: the joint solution of the crystallographic structure of light harvesting complex II based on a computational search model; the explanation of the mechanical properties of titins immunoglobulin domains through mutants suggested by computational modeling; the explanation of the mechanism of water conduction and proton exclusion in aquaporins

The preparation of this report was coordinated by Tim Skirvin

based on a combination of crystallographic and computational approaches, an achievement cited by the Nobel Foundation in connection with Agre's Nobel prize in Chemistry last year; and most recently an investigation of structure and mechanism of fibronectin-III that controls key properties of the extracellular matrix, preventing metastasis of cancer cells and wound healing, in which case computations and NMR spectroscopy jointly revealed a key protein structure. Collaborating experimental groups have become already self-sufficient in regard to the computational expertise and infrastructure, carrying out computational-experimental projects now on their own. This we consider our greatest achievement.

The Resource for Macromolecular Modeling and Bioinformatics, existing now since fifteen years, is presently in the most active phase of its development. Opportunities are driving all our efforts at an unprecedented pace: the proliferation of high end graphics to commodity desktop computers makes our graphics tools a household item for laboratory scientists with over 40,000 registered users; the advent of teraflop computers powered by hundreds and soon thousands of processors and of commodity computer clusters, a platform for which our modeling software was specifically designed, turned our NAMD program into a research instrument adopted every day by more users, now counting in the thousands; the access grid connecting research computers in the US and worldwide is uniquely employed by our communication and collaboration program BioCoRE seemlessly linked to VMD and NAMD; last, but not least, the revolutionary pace of the discovery of essential, but huge biomolecular structures in the cell that all require our tools because of their size and complexity. The by now often demonstrated reliability of modeling makes the tools of our resource invaluable life science instruments today.

This document reports research and development efforts in our Resource during the past year. What it does not report is the high level of activity and enthusiasm among our ranks that leads the Resource into a prosperous future. Our development teams are working on a new generation of modeling software that combines sequence and structure analysis; our researchers are involved in a record number of new and exciting collaborations that open new frontiers in cell biology; our faculty has just initiated a series of hands-on training courses in which participants learn molecular modeling and bioinformatics "by doing"; our technical staff has made great progress in building the computer laboratory of our Resource into a powerful research instrument beyond our imagination even few years ago.

# Highlights

## Proton Blockage in Aquaporins

In 2003, Peter Agre shared the Nobel prize in chemistry, for his ground breaking discovery of water channels called aquaporins (AQPs)* [1]. The successful characterization and exploration of AQPs were the results of efforts of many experimental researchers. Theoretical calculations and computer simulations, however, played a major role in explaining structure-function relationship and, most importantly, the mechanism of selective function of these channels. In particular, the mechanism by which these passive water pores manage to keep protons out of the cell, which was puzzling biologists since the discovery of the first AQP, was elegantly described by the simulations.

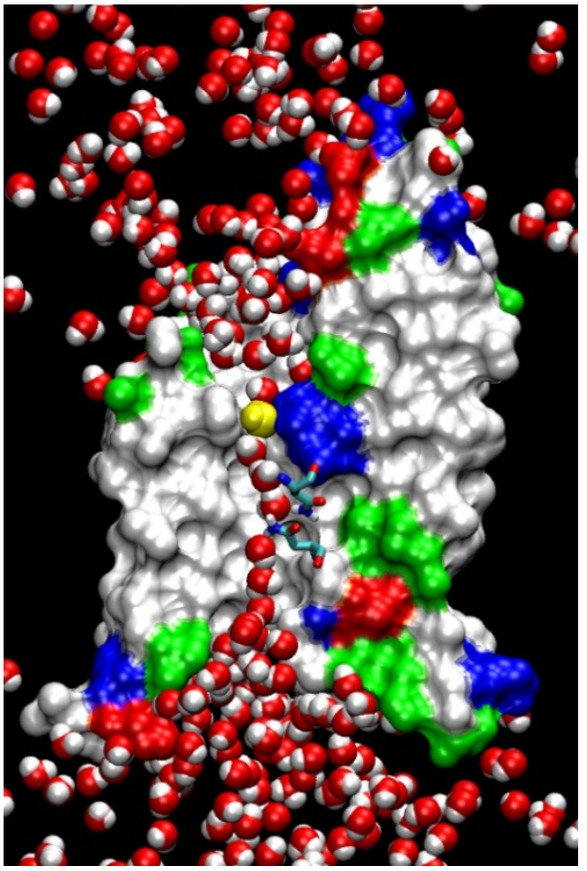

Figure 1: Single-file water in aquaporins. Water molecules flip in the middle of the channel, and thus create an arrangement that prevent proton leak through the channel.

AQPs provide an efficient means of fast transport of water across the cell membrane [2–4]. They are widely distributed in all domains of life, including bacteria, plants, insects, and vertebrates [2–4], and play a critical role in water homeostasis of the cell. In the human body, more than ten different AQPs have been found in various organs, such as red blood cells, kidneys, salivary glands, lungs, the eyes, and the central nervous system. Despite the short history of AQP research, certain types of several diseases, including congenital

*URL: `http://www.ks.uiuc.edu/Research/aquaporins/`

cataracts, Sjorgen's syndrome, and nephrogenic *diabetes insipidus*, have been associated with impaired function of these channels [2, 4].

Biological cells can be viewed as batteries carrying a voltage difference across their cell membrane. A major source of the voltage is a gradient of protons, which is physiologically used by the cell as a source of energy to drive such key cellular processes as ATP synthesis. Leakage of protons through membranes, therefore, would have a lethal effect on cells. This seemed to generate a problem for AQPs, since a single AQP channel is capable of exchanging hundreds of millions of water molecules between the two sides of the membrane every second, and protons are known to use water as a transport medium such that a fast water channel like AQP should completely drain the cellular battery.

Earlier molecular dynamics simulations of AQPs [5] solved this puzzle, revealing a novel mechanism for proton exclusion of AQPs through a unique arrangement of water molecules inside the channel's internal electrostatic forces: a bipolar orientation of water molecules in AQPs in which water molecules flip at the center of the channel. This orientation pattern is highly unfavorable for proton transfer. The mechanism was examined further through several studies investigating the details of electrostatic forces in AQPs, which verified that the bipolar orientation arises from the electric field generated by the channel [6].

In collaboration with leading experts, the energy associated with the transfer of a proton through AQPs [7, 8], a task that combined quantum mechanical and classical MD simulations, was calculated. Proton transfer was artificially induced by forcing a proton to visit all regions of the channel, and the energy calculated. Both studies [7, 8] found high energy barriers against permeation of a proton through the channel with a maximum at the center of the channel, thus verifying the originally proposed mechanism of proton exclusion by AQPs [5]. Through a fine tuned electrostatic mechanism contributed by several parts of the protein, AQPs provide selective conduits for water transport without allowing protons to permeate.

The Resource continues to study other transport features of AQPs. Recent papers include a detailed study of pressure induced water permeation through mammalian AQP1 [9], and investigation of the mechanism of glycerol transport through bacterial aquaporin GlpF [10, 11].

## Mechanical properties of fibronectin

Tissues of the human body are composed of specialized cells held together by a connective fabric of proteins that form the knots of a net glueing cells together. Upon stretching tissues, the knots unravel, rendering the net larger, but mysteriously also firmer. Fibronectin (FN) is one of such proteins that responds to mechanical forces by forming fibrils through partially unfolding its modules.* As one of the extracellular matrix (ECM) proteins, FN molecules act as an adhesive connecting to cells in a tissue and guiding cell migration [12]. Stretching of FN fibrils unfolds individual FN-III modules, their major molecular component [13]. The unfolding of FN-III modules, provides the necessary extension to the FN fibril that can be stretched four times its relaxed length [14]. In addition, the unfolding of FN-III modules mediates fibrillogenesis by exposing otherwise buried cryptic sites [15].

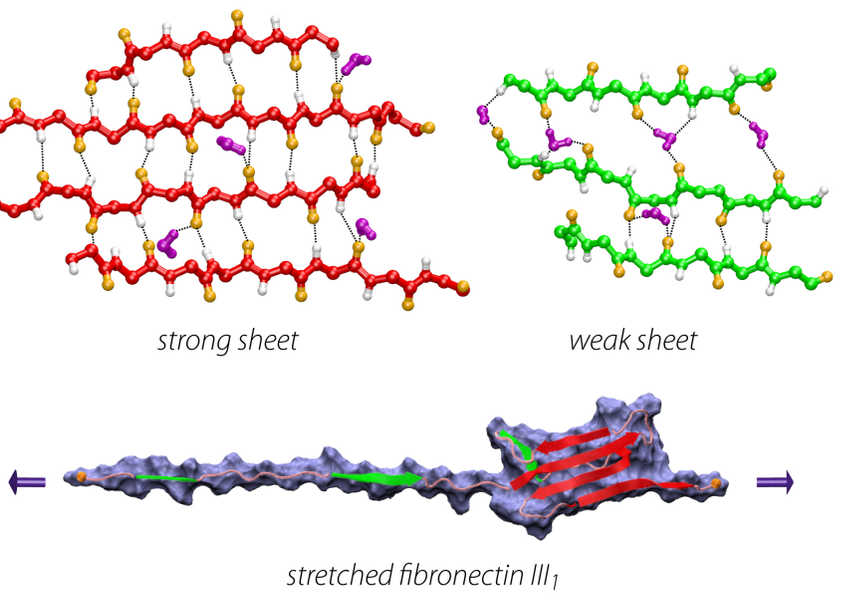


Figure 2: Structures of the FN-III$_1$ module. The module consists of two $\beta$-sheets (upper two snapshots) with different mechanical design. The weaker $\beta$-sheet unravels first when a force is applied to the termini of the module. The module then becomes a stable intermediate (lower snapshot) with the stronger $\beta$-sheet largely intact. Hydrophobic residues exposed in this intermediate bind to other fibronectin modules, thereby enabling the self assembly of fibronectin molecules.

Evidence accumulated from thermal, chemical [16–18] or mechanical unfolding experiments [19] suggested that the first FN-III module, FN-III$_1$, undergoes certain conformational changes to a partially unfolded intermediate that induces the fibronectin assembly. Furthermore, a 76 amino acid fragment from FN-III$_1$, termed anastellin and obtained by excising an N-terminal portion of the module, was found to be structurally stable and to promote fibronectin self-association, thereby inhibiting the growth of cancer cells [20]. However, the structure of this FN-III$_1$ and its intermediate remained elusive.

*URL: `http://www.ks.uiuc.edu/Research/mechanicals/`

In collaboration with experimental groups (I. Campbell, Oxford; V. Vogel, U. Washington), we have determined the NMR structure of FN-III$_1$ and modeled the module's mechanical unfolding pathway using steered molecule dynamics simulations [21] (Fig. 2). Homologous to other structurally solved FN-III modules [22, 23], FN-III$_1$ consists of two four-stranded $\beta$-sheets packed into a motif called $\beta$-sandwich. Unlike most other FN-III modules, however, a well conserved proline residue is missing in one of the $\beta$-sheet. This mutation extends the inter-strand hydrogen bonding network of the $\beta$-sheet, which becomes much more stable. Stretching of the molecule unravels first the weaker $\beta$-sheet, extends FN-III$_1$ by $\sim$100 Å, and leads to a stable intermediate with the stronger $\beta$-sheet yet unraveled. The intermediate was seen also in atomic force microscopy experiments [19], and explains the role of anastellin in preventing tumor metastasis [24].

## *Lac* Repressor-DNA Loop Dynamics

The *lac* repressor protein is the most widely known regulatory protein that helped to establish the paradigm of gene control through protein-DNA interaction [25]. The protein functions as a negative switch that clamps DNA and induces a loop in a key DNA segment, which contains the promoter for a set of genes, *lacZ, lacY* and *lacA*, coding for proteins involved in lactose uptake and metabolism [26, 27]. In the absence of lactose, the protein binds with high specificity to two 21 bp DNA segments [28] folding the DNA between them into a loop (Fig. 3), and inhibiting the expression of genes *lacZ, lacY* and *lacA* [29]. The formation of the loop has been shown to be critical for full repression [30]. When lactose is present, the repressor dissociates from the DNA, allowing the transcription of the genes [25].

Studying the dynamics of the *lac* repressor-DNA complex is important for understanding the mechanisms of gene control. However, all-atom computer simulation of the complex is unfeasible, since including in such simulation the long DNA loops formed when a single protein binds simultaneously to two distant DNA sites (see Fig. 3) results in a system with a million of atoms, yet beyond the reach of available computing power.

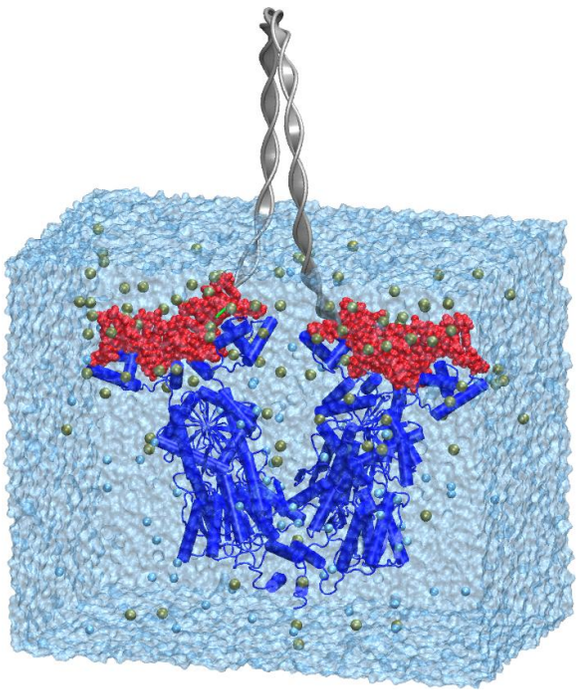

Figure 3: Multi-scale simulation of the *lac* repressor-DNA complex. The box represents the system modeled by MD, including the *lac* repressor bound to two 19 bp DNA segments, placed in a water box with sodium and chloride ions (230,000 atoms). The loop arising from the box represents the DNA loop modeled by means of elasticity theory. The multi-scale method combines these two models into a cogent description, as explained in the text.

The Resource developed a multi-scale approach* to link a full atom simulation of protein and DNA with a continuum-level description of the DNA loop [31]. The method builds a coarse-grained model of the DNA loop to determine DNA geometry and energy, as well as the forces of the protein-DNA interaction. This method is based on the theory of elasticity and takes into account the bending anisotropy and electrostatics of DNA [32, 33]. The forces obtained are then incorporated to the molecular dynamics simulations of the DNA binding protein (*lac* repressor) that does not explicitly include the DNA loop. Iterative rounds of molecular dynamics alternated with recomputing the elastic force from the DNA loop providing a dynamic picture of the *lac* repressor-DNA complex system.

The simulation revealed the mechanical properties of the *lac* repressor in complex with DNA and how its architecture is perfectly attuned to the task of controlling the DNA in a loop form. A significant rotation of the head groups was observed, suggesting that this motion is the principal degree of freedom of the protein. The *lac* repressor seems to exert its control over the DNA by binding with its two head groups strongly to the DNA and through an extreme flexibility not to let go of it. The simulations encompassing effectively a one million atom biomolecular system open a new era of so-called multi-scale computational modeling of biomolecules.

The possibility of the protein to exist in an open conformation about the bottom "hinge" region has been proposed by experiments. The simulations so far show a slight opening of the protein about this region. These findings will be compared with experiment based-models of repression. Further investigation into the open structure of the *lac* repressor-DNA complex is in progress.

*URL: `http://www.ks.uiuc.edu/Research/pro_DNA/elastic`

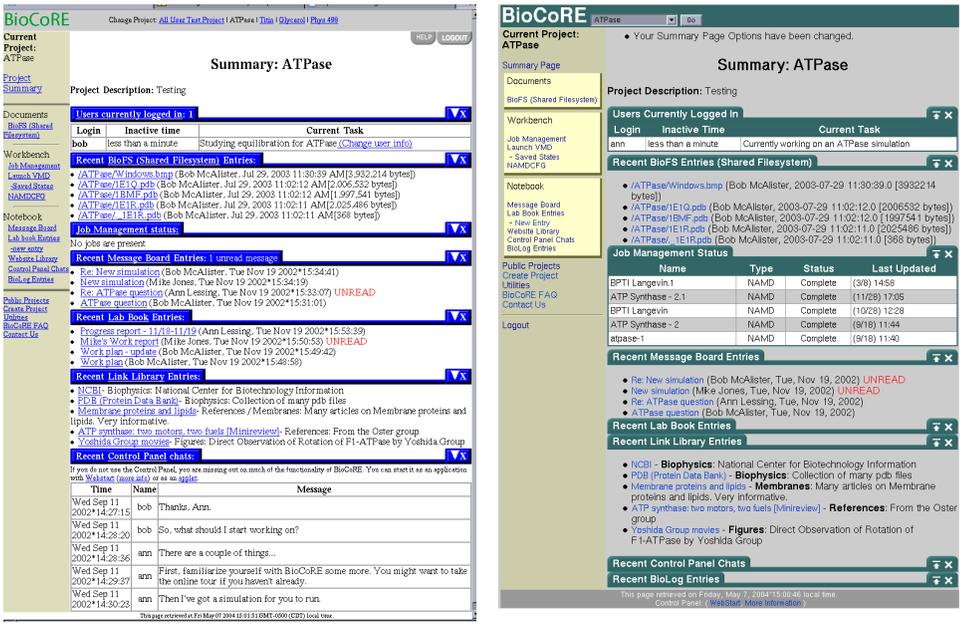


Figure 4: Previous version of the BioCoRE interface is shown on the left. The new version is shown on the right.

## BioCoRE Improvements for Collaborations Between Researchers

One objective of the Resource is to develop and maintain collaboration software for use within the biomedical community. Excellent progress has been made in the past year through BioCoRE* (the *Bio*logical *Co*llaborative *R*esearch *E*nvironment), a collaborative work environment for biomedical research, research management and training. BioCoRE offers scientists, working together or alone, a seamless interface to a broad range of local and remote technologies such as discipline-specific and general tools, data, and visualization solutions. To streamline collaboration across temporal and geographic distance, BioCoRE provides transparent access to technological resources (hardware and software) and databases. BioCoRE features powerful yet easy-to-use tools, among them co-authoring papers and other documents, running applications on supercomputers, sharing molecular visualizations over the Internet, notifying project team members of recent project changes by email, chatting, keeping a lab book, and other practical features.

The Resource has implemented a completely redesigned BioCoRE interface and codebase. This new interface, (Figure 4), gives BioCoRE a much more intuitive look and feel, which will help with adoption by the scientific community. Underlying the user-interface refinements are extensive revisions in the BioCoRE code to take advantage of recent advances in web development. The entire codebase has been refactored to simplify the future development of new modules and extensions for BioCoRE.

To more thoroughly integrate BioCoRE into their scientific workflow, researchers want to

*URL: `http://www.ks.uiuc.edu/Research/biocore/`

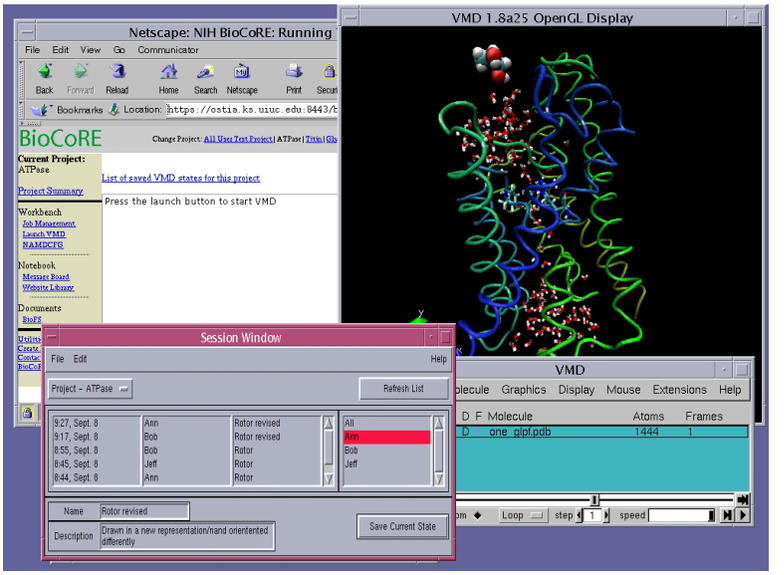


Figure 5: New VMD launcher in operation in the lower left corner.

script and programmatically interact with BioCoRE from their own programs and interfaces. In response to these needs and to trends in the use of the Resource's other flagship programs, VMD and NAMD, the redesign includes a more comprehensive Application Programming Interface (API), which is being used for Control Panel communications with the BioCoRE server. Because the API is using the industry standard XML communication language, any interested researcher could duplicate the functionality of the Control Panel (instant messaging and notification) in their own program.

Growing user interest in realtime collaborative sessions has prompted an extensive revision of the VMD Saved State module. The new inteface for the VMD BioCoRE tool, shown in Figure 5 provides "one-click" state saving which makes it considerably easier to share views with collaborators over a distance within a few seconds time. Many of the pieces of information that users formerly provided to the tool are now automatically filled in which makes it more efficient for researchers to use the tool as a part of their normal work patterns.

## Summer School on Theoretical and Computational Biophysics


Figure 6: Summer School Class of 2003

The Resource hosted a two-week Summer School* from June 2-13, 2003 designed to introduce a wide range of physical modeling and computational approaches used for the simulation of biological systems and the investigation of their function at an atomic level. The workshop was designed for graduate students and postdoctoral researchers in biophysical fields to extend their research skills to include computational and theoretical expertise, as well as other researchers interested in theoretical and computational biophysics.

Modeling the molecular processes of biological cells is a craft and an art. Techniques like theoretical and computational skills can be learned by training, but meaningful applications are achieved only with experience and sensitivity. The Summer School in Theoretical and Computational Biophysics attempted to teach both the craft and art of modeling through learning by doing: nearly a hundred participants from all over the world came for two weeks to the Beckman Institute to stretch proteins, pull water through molecular channels, mine genomic data, build their own computer cluster, and study their favorite biomolecules. After lectures and discussions in the morning, afternoon and evening sessions were devoted to learning by doing, assisted by 300 pages of tutorials, in computer laboratories humming with computational biology software, such as VMD, NAMD, and GAMESS, and linked to NCSA's fast multiprocessor machines.

Lectures were given throughout the two-week course, on topics ranging from statistical mechanics of proteins to modeling large systems. Resource members and guest lecturers lent their expertise with talks that started with introductory molecular biophysics mate-

*URL:`http://www.ks.uiuc.edu/Training/SumSchool/`

rial, then advanced to more in-depth material involving molecular dynamics, numerical methods, and large system modeling. The hands-on laboratory tutorials in the afternoons gave students the chance to use the information learned in the morning lectures. The tutorials were newly written for the Summer School; the preparation helped Resource members to clarify and improve software documentation. The students were trained in using molecular modeling and analysis software, then later were able to use that knowledge to perform simulations. Students were immediately able to apply what they learned over the two weeks to their own research projects. Labs were also available in the evening for students to continue work on the tutorials or on their own projects. There was even a "molecular beauty contest"[†] at the conclusion of the Summer School for students to showcase the research projects they had worked on over the previous two weeks. There were also hands-on workshops on building a computing cluster, so that students could return to their research groups after the summer school and build computing environments to readily handle the computing tasks they learned about.

A full and detailed evaluation was taken after the summer school, to discover the effectiveness of the learning methods. Students answered survey form questions about the teaching methods, techniques, and material in general[‡], as well as individual lectures and tutorials[§]. Results were positive; nearly all students stated they gained much from the school.

Education is a continuous process. Not only must researchers continue to learn, but also to teach others. The knowledge that students took with them from the summer school will be passed on to others. The school, funded by NSF and NIH, may have lasted only two weeks, but will go on much longer: all school materials remain available on the web, and participants will use BioCoRE to stay in touch and continue the scholarship and friendship experienced in Illinois.

[†]URL:http://www.ks.uiuc.edu/Training/SumSchool/BeautyContest.html

[‡]URL:http://www.ks.uiuc.edu/Training/SumSchool/questionnaire1A.html

[§]URL:http://www.ks.uiuc.edu/Training/SumSchool/eval/ltEval.html

# Scientific Subprojects

BTA UNIT: C

TITLE: Chemomechanical energy coupling in $F_1$-ATP Synthase

KEYWORDS: Bioenergetics, ATP synthesis, ATP hydrolysis, energy conversion, molecular motor, domain motion, electrostatic interactions, multiscale modeling, molecular dynamics

AXIS I: 2

AXIS II: 74C 74H 89

INVEST1: Israelewitz, Barry
DEGREE1: M.A.
DEPT1: Biophysics
NONHOST1:

INVEST2: Dittrich, Markus
DEGREE2: M.A.
DEPT2: Physics
NONHOST2:

INVEST3: Kleinekathöfer, Ulrich
DEGREE3: Ph.D.
DEPT3: Institute of Physics
NONHOST3: Chemnitz U. of Tech., Germany

INVEST4: Hayashi, Shigehiko
DEGREE4: Ph.D.
DEPT4: Fukui Inst. Fundamental Chem.
NONHOST4: Kyoto University

INVEST5: Weber, Joachim
DEGREE5: Ph.D.
DEPT5: Cell Biol. and Biochem.
NONHOST5: Texas Tech U. Health Sciences Center

% BTA $: 5%

% BTA for AIDS $: 0%

ABSTRACT: The enzyme $F_1$-ATPase* is a molecular motor that converts the chemical energy stored in the molecule adenosine tri-phosphate (ATP) into mechanical energy via rotation of its central stalk. $F_1$ consists of a hexamerically arranged ring of alternating $\alpha$ and $\beta$ subunits that contain the three catalytic binding sites, and a central stalk made up of the $\gamma$, $\delta$, and $\epsilon$ units. *In vivo*, $F_1$ constitutes the solvent-exposed portion of the enzyme $F_1F_o$-ATP synthase and, as part of the holoenzyme, can also work in reverse, i.e., convert rotation into the synthesis of ATP.

The Resource has pursued two approaches to examine the large scale mechanical changes which couple torque application at the $F_1$ central $\gamma\delta\epsilon$-stalk to binding site changes at the $\beta$ catalytic sites. In the first approach, a 327,000-atom all-$F_1$ system (solvated $\alpha_3\beta_3\gamma\delta\epsilon$ domains) was simulated [34], with a torque applied at the putative $F_o$ interface to constrain the central stalk to 24 °/ns rotation. A purpose-built NAMD [35] function provided the required constant-angular velocity constraints. Several subunit-subunit interactions, as well as conformational changes at the catalytically-active $\beta_{TP}$ site, consistent with a cooperative binding-change model of ATP synthesis [36], were observed. The simulations revealed how a series of ionic bridges between the rotating central stalk and the $\alpha_{TP}$ subunit moves the $\alpha_{TP}$ 402–411 loop against the the $\beta_{TP}$ site, possibly helping to force open $\beta_{TP}$, as required for performing ATP synthesis.

In the second approach, single $\beta$ subunits were examined in isolation, surrounded only by solvent or neighboring $\alpha$ subunits (as 80,000 – 130,000 atom systems), in order to examine the innate tendencies towards conformational change of the $\beta$ subunits when removed from the rest of $F_1$. Several combinations of starting crystal structure and nucleotide population were simulated, encompassing both $\beta$ closing (two domains of $\beta$ moving together during torque-generating hydrolysis) and $\beta$ opening ($\beta$ domains moving apart during torque-utilizing synthesis). The $\beta$-closing experiments demonstrated spontaneous closing motions on a 10 ns time scale; most can be decomposed into a small in-plane scissoring motion and a larger out-of-plane pivoting motion.

To investigate how the catalytic sites achieve efficient catalysis and are able to couple ATP hydrolysis to mechanical rotation, the Resource has conducted *ab initio* quantum mechanical/molecular mechanical simulations of ATP hydrolysis in the catalytic sites of $F_1$-ATPase [37]. Density functional theory was employed for the quantum mechanically treated sub-system to investigate both the $\beta_{TP}$ and the $\beta_{DP}$ catalytic sites, thereby, greatly improving the accuracy of a previous study [38]. The simulations revealed a drastic change in the energetics of ATP hydrolysis in going from $\beta_{TP}$ to $\beta_{DP}$. This was found to be largely due to movement of the so

*URL: `http://www.ks.uiuc.edu/Research/atpase/`

called arginine finger residue $\alpha$R373 in agreement with experimental findings. A multi-center proton relay mechanism was found to be responsible for efficient ATP hydrolysis stressing the importance of a pre-organized solvent environment in the catalytic sites.

BTA UNIT: C

TITLE: Energy conversion in $F_o$-ATP Synthase

KEYWORDS: Bioenergetics, ATP synthesis, ATP hydrolysis, energy conversion, molecular motor, proton transfer, domain motion, electrostatic interactions, membrane protein, multiscale modeling, molecular dynamics, stochastic model

AXIS I: 2

AXIS II: 74H 89

INVEST1: Aksimentiev, Aleksei
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Balabin, Ilya
DEGREE2: Ph.D.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: Kanchanawarin, Chalermpol
DEGREE3: M.A.
DEPT3: Physics
NONHOST3:

INVEST4: Fillingame, Robert
DEGREE4: Ph.D.
DEPT4: Biomolecular Chemistry
NONHOST4: U. of Madison Medical School

% BTA $: 4%

% BTA for AIDS $: 0%

ABSTRACT: $F_1F_o$-ATP synthase* is a large protein complex that efficiently converts a transmembrane electrochemical potential into chemical energy by synthesizing adenosine tri-phosphate (ATP) from adenonsine di-phosphate and organic phosphate. It consists of $F_o$ and $F_1$ sub-units, two rotary molecular motors that are coupled to each other through an elastic central stalk. The $F_o$ sub-unit is an integral membrane

*URL: `http://www.ks.uiuc.edu/Research/atpase/`

protein complex that converts the transmembrane proton gradient into rotation of the central stalk. This rotation drives cyclical conformation changes in the binding pockets of the solvent exposed $F_1$ unit eventually leading to the synthesis of ATP. Remarkably and in contrast to other molecular motors, $F_1F_o$-ATP synthase can also work in reverse and use the energy stored in ATP to generate a transmembrane proton gradient.

The mechanism of the unidirectional rotation of $F_o$ is not known. Recent experiments [39, 40] have shown that proton translocation through $F_o$ is coupled to large structural rearrangements, suggesting that its modeling will require long time scale and large atomic-scale MD simulations. Using the program NAMD2 [35], the Resource has performed the first ever molecular dynamics simulations of $F_o$ [41]. The simulations were complemented by a mathematical model capable of describing processes on a physiological time scale. In this stochastic mathematical model, the state of the system was characterized by several essential degrees of freedom: rotation of the *c* subunit ring, rotation of the individual transmembrane helices at the rotor/stator interface, and protonation states of principal residues. The key processes considered in the stochastic model were investigated by molecular dynamics, which included all-atom simulations of the *c*-ring rotation as well as the rotation of individual transmembrane helices at different protonation states of the principal residues. A salt bridge between residues of *a* and *c* subunits was observed; transfer of the salt bridge from one *c* subunit to another was found to be critical for $F_o$ operation. Our model also predicts that the *c*-ring rotation takes place in steps; this prediction is being tested experimentally by our collaborator.

BTA UNIT: C

TITLE: Sequencing DNA with a nanopore device

KEYWORDS: DNA sequencing, silicon biotechnology, nucleic acids, nanotechnology, bio-sensors

AXIS I: 2 9

AXIS II: 39 52 74G

INVEST1: Aksimentiev, Aleksei
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Chu-Cruz, Eduardo
DEGREE2: B.Sc.
DEPT2: Biophysics
NONHOST2:

INVEST3: Timp, Gregory
DEGREE3: Ph.D
DEPT3: Beckman Insitute
NONHOST3:

INVEST4: Leburton, Jean-Pierre
DEGREE4: Ph.D
DEPT4: Beckman Insitute
NONHOST4:

% BTA $: 4%

% BTA for AIDS $: 0%

ABSTRACT: Devices that incorporate both proteins and silicon electric circuits have the potential to revolutionize biomedical sciences. Already today, the miniaturization of silicon technology makes it possible to manufacture electronic circuits with features comparable in size to the building blocks of life: proteins and DNA. Thus, a putative device for reading the genetic information encoded in DNA could be built around a tiny pore in a thin (2-5 nm) silicon membrane. The chemical sequence of a DNA strand can be discerned by such a device, in principle, through a semiconductor detector integrated with the pore that would record the electrical signal induced

by the DNA molecule transiting the pore. To complement ongoing experimental studies developing such pores and measuring signals in response to the presence of DNA (Gregory Timp, UIUC), the Resource has been conducting MD simulations of DNA translocation through nanopores*.

To simulate the DNA/nanopore system, the Resource has extended the methodology of microscopic simulations developed for membrane proteins [5, 10, 41–46]. A molecular force-field describing water, ions, and nucleic acids [47] was combined with the MSXX force-field [48] developed for silicon nitride. Unique features of the NAMD2 program [49] allowed the Resource to carry out high-performance simulations of such an unusual system accounting for up to 170,000 atoms.

The results suggest that the rate-limiting step for the DNA translocation is not the actual transit of DNA through the pore, but rather the search for an initial conformation that facilitates the translocation. Hydrophobic interactions between DNA bases and the pore surface can slow down translocation of single stranded DNA and might favor unzipping of double stranded DNA inside the pore. Current blockades induced by DNA occluding the pore mouth, but not transiting the pore, were found to have the same magnitude as the blockade observed when DNA transits the pore. The actual translocation of DNA through the nanopore is predicted to have a rate of 2-10 nm/$\mu s$, implying that, in order to enable a single nucleotide resolution, the semiconductor device recording the electrical signatures should be designed to have a 1 GHz bandwidth. Two papers discribing these studies have been submitted [50, 51].

*URL: `http://www.ks.uiuc.edu/Research/nanopore/`

BTA UNIT: C

TITLE: Excitation transfer dynamics in trimeric photosystem I

KEYWORDS: bioenergetics, photosynthesis, excitation transfer, excitation sharing, robustness, optimality

AXIS I: 7A 8 9

AXIS II: 74H 77 84

INVEST1: Şener, Melih K.
DEGREE1: Ph. D.
DEPT1: Beckman Institute
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INVEST2: Park, Sanghyun
DEGREE2: Ph. D.
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INVEST3: Lu, Deyu
DEGREE3: B. S.
DEPT3: Physics
NONHOST3:

INVEST4: Damjanović, Ana
DEGREE4: Ph. D.
DEPT4: Biophysics
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INVEST5: Ritz, Thorsten
DEGREE5: Ph. D.
DEPT5: Physics and Astronomy
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INVEST6: Fromme, Petra
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% BTA $: 4%

% BTA for AIDS $: 0%

ABSTRACT: Bioenergetic processes in photosynthesis and in the respiratory chain of mammals are carried out by homologous enzymes. Therefore, the study of energy and charge transfer processes in photosynthetic organisms provides insight for similar processes in eukaryotic mitochondria. In oxygenic species, such as plants, algae and cyanobacteria, the first step of energy transformation, the capture of light followed by a transmembrane charge separation, is performed by two large membrane proteins, photosystem I* (PSI) and photosystem II (PSII). The 2.5 Å resolution structure for the PSI complex from the cyanobacterium *Synechococcus (S.) elongatus* [52], published by our collaborator Petra Fromme (Arizona State University), reveals 96 chlorophylls and 22 carotenoids comprising an antenna array. A peculiar feature of cyanobacterial PSI is its occurrence in both monomeric and trimeric forms depending on growth conditions. This is in contrast to plant PSI, which is observed only in monomeric form. Mutagenesis studies in *S. elongatus* have shown that the trimerization is essential for the growth of the cells at low light intensity [53, 54], which corresponds to the light intensity in the natural habitat.

In the past funding period the Resource has continued its collaboration with Petra Fromme to study the excitation transfer dynamics in photosystem I in its trimeric form, containing a large network of 288 chlorophylls. A recent publication by the Resource [55] introduced a structure-based description for excitation migration in multi-reaction center light harvesting systems. The description is an extension of the sojourn expansion [56], which decomposes excitation migration in terms of repeated detrapping and recapture events. The approach is applied to light harvesting in the trimeric PSI. Excitation is found to be shared between PSI monomers and the chlorophylls providing the strongest respective links are identified. Excitation sharing is investigated by computing cross-monomer excitation trapping probabilities. It is seen that on the average there is a nearly 40% chance of excitation cross-transfer and trapping, indicating efficient coupling between monomers. The robustness and optimality of the chlorophyll network of trimeric PSI is also examined. Even though the peripheral antenna geometry is seen to be optimal for maximizing the quantum yield, the geometry of the inter-monomer boundary chlorophylls are seen to be not particularly optimized for facilitating maximal excitation sharing.

*URL: `http://www.ks.uiuc.edu/Research/ps1`

BTA UNIT: T

TITLE: Substrate Permeation and Selectivity in Aquaporins

KEYWORDS: Aquaporin, aquaglyceroporin, water channel, membrane protein, water permeation, proton transfer

AXIS I: 2

AXIS II: 74H 89

INVEST1: Tajkhorshid, Emad
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INVEST2: Zhu, Fangqiang
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INVEST3: Lu, Deyu
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INVEST4: Grayson, Paul
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INVEST5: Yu, Jin
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DEPT5: Physics
NONHOST5:

INVEST6: Jensen, Morten
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INVEST7: Chakrabarti, Nilmadhab
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INVEST8: Pomes, Regis
DEGREE8: Ph.D.
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DEPT9: Biochemistry
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INVEST10: Ilan, Boaz
DEGREE10: Ph.D.
DEPT10: Chemistry
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INVEST11: Voth, Gregory
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% BTA $: 6%

% BTA for AIDS $: 0%

ABSTRACT: Aquaporins (AQPs)* are a family of membrane channels facilitating water permeation across biological membranes [1]. In addition to water, some AQPs also conduct other neutral molecules, such as linear sugars and urea [2, 57]. Charged species, however, cannot be conducted through AQPs. Particularly interesting is the fact that even protons, which can be readily transferred through hydrogen bonded chains of water, are also efficiently blocked [58]. The impaired function of AQPs is associated with pathophysiological conditions, such as *diabetes insipidus* [2] and congenital cataracts. The Resource has continued to investigate the mechanism of transport of various substrates and the selectivity features employed by these channels through molecular dynamics (MD) simulations [34].

*URL: `http://www.ks.uiuc.edu/Research/aquaporins/`

In order to shed light onto the mechanism of stereoselective substrate permeation in AQPs, conduction of two sugar stereoisomers, ribitol and arabitol, through a bacterial GlpF was studied using interactive molecular dynamics, a novel technique that allows the user to interact with the simulation in real-time [10]. The study revealed how formation of an increased number of hydrogen bonds between the substrate and the channel accounts for an almost 10-fold difference in the permeation rates between these different sugar molecules. In a different study, a theoretical model (the "six-step model") based on non-equilibrium statistical mechanics was proposed to quantitatively characterize glycerol transport in GlpF [11]. The study was the first to show how structural asymmetry of channels may contribute to an increased rate of substrate permeation in only one direction, namely the physiologically relevant one.

Water permeation in AQPs was investigated [59] through both simulations and theoretical models. A new method was used to induce a hydrostatic pressure difference across the membrane in MD simulations. The osmotic permeability ($p_f$) of AQP1 calculated using this method [9] agrees well with experiments. Furthermore, by employing a continuous-time random-walk model [60], we derived a quantitative relationship between the osmotic permeability ($p_f$) and diffusion permeability ($p_d$) of single-file water channels [9]. The Resource has also proposed a collective diffusion model for water permeation [61] that can be applied to any water channel. This model can be used to calculate $p_f$ from equilibrium MD simulations. As a simplified model of water channels, we have also studied water diffusion and orientation in pure and chemically modified nanotubes [62].

To continue our investigation of the mechanism of proton exclusion in AQPs, and in order to verify the mechanism put forward in our earlier studies [5], the Resource has further analyzed electrostatic effects in AQPs [6] and calculated the energy barrier against proton transfer in two collaborative studies applying different methodologies [7, 8]. These investigations confirmed that the electric field inside the channel accounts for the unique bipolar water orientation observed in AQPs [6]. Explicit simulations of proton transfer [7, 8] indicated that the main barrier against the permeation of protons through the single file of water formed inside the channel resides at the midpoint of the channel, where water molecules are forced to flip their dipole moment, and thus verified our proposed mechanism [5].

BTA UNIT: C

TITLE: Mechanical properties of fibronectin

KEYWORDS: fibronectin, fibrillogenesis, steered molecule dynamics, unfolding, integrin

AXIS I: 4 14

AXIS II: 74H 89

INVEST1: Gao, Mu
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INVEST2: Craig, David
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% BTA $: 5%

% BTA for AIDS $: 0%

ABSTRACT: Fibronectin (FN) forms fibrillar networks coupling cells mechanically to their environment and to neighboring cells, providing a substrate for anchorage and guiding cell migration during embryonic development and wound healing [12]. The formation of FN fibrils, fibrillogenesis, is a tightly regulated process involving the exposure of cryptic binding sites in individual FN type III (FN-III) repeats presumably exposed by mechanical tension. The FN-III$_1$ module has previously been proposed to contain such cryptic sites that promote the assembly of extracellular matrix FN fibrils. In collaborating with experimental groups, we have combined NMR and steered molecular dynamics (SMD) simulations to study the structure and mechanical unfolding pathway of FN-III$_1$ [21]. * The study finds that FN-III$_1$ consists of a $\beta$-sandwich structure that unfolds to a mechanically stable intermediate which is about four times the length of the native folded state. Considering previous experimental findings, our studies provide a structural model by which mechanical stretching of FN-III$_1$ may induce fibrillogenesis through this partially unfolded intermediate.

Extending previous SMD studies on FN-III modules [63–66], we have probed the mechanical stability of all structurally known FN-III modules [67]. The studies suggest that the mechanical stability of FN-III modules can be tuned through substitutions of just a few key amino acids by altering access of water molecules to inter-strand hydrogen bonds that break early in the unfolding pathway.

FN-III modules bind to integrin, a transmembrane receptor protein that mechanically transmit forces generated in cytoskeleton to extracellular matrix. Recently, the first crystal structures of the extracellular portion of integrin $\alpha$V$\beta$3, in both liganded and unliganded forms, have been reported, providing an opportunity to investigate how integrins bind and interact with fibronectin [68, 69]. We have used MD to study the stability of the Arg-Gly-Asp ligand and the integrin [70]. The simulations reveal that divalent cations stabilize receptor-ligand interactions against force-induced dissociation through water-mediated process.

*URL:`http://www.ks.uiuc.edu/Research/mechanicals/`

BTA UNIT: T, C

TITLE: *Lac* Repressor-DNA loop dynamics

KEYWORDS: multi-scale, coarse-grained, elastic rod, DNA, *lac* repressor, molecular dynamics, gene control, genetic switch, protein-DNA interaction

AXIS I: 2 7a 9 28 (Gene control)

AXIS II: 42 74g 74h 77 89

INVEST1: Alexander Balaeff
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DEGREE2: Ph.D.
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% BTA $: 2%

% BTA for AIDS $: 0%

ABSTRACT: DNA structure is extensively manipulated by proteins. Protein-DNA complexes arise in many different contexts in the cell, and the resulting interactions are important in all aspects of life. One example of protein-DNA interaction involves the storage and expression of genetic information. Modeling of protein-DNA interactions calls for a multi-resolution approach, because the size of the DNA chain interacting with a protein is often significantly larger than the protein itself. For such large complexes, all-atom computer simulation is unfeasible. One classic example is the *lac* repressor protein, that has been the paradigm of gene control for the past 50 years. In this case, the protein binds simultaneously to two distant DNA sites, forming DNA loops of either 76 of 384 base pairs (bp). The resource has developed a multi-scale method for modeling protein-DNA complexes* that combines two levels

*URL: `http://www.ks.uiuc.edu/Research/pro_DNA/elastic`

of description: the elastic rod model is used to build the equilibrium structure of the DNA loop, and MD is used to simulate the dynamics of the protein. The structure obtained from the MD simulations provides the boundary conditions for the elastic rod calculation. The forces and torques that the loop would exert on the protein are obtained from the rod calculation and included in the MD simulation using the Steered Molecular Dynamics approach. This iteration between both descriptions was performed every 10ps of the MD run. The multi-scale method was used to investigate the structure of the *lac* repressor in complex with the DNA. An all-atom structure of the *lac* repressor bound to two short pieces of DNA was constructed by combining several NMR and crystal structures and equilibrated. However, none of the available structures contained the DNA loop induced by the protein.Using a coarse-grained elastic rod model, it was possible to predict a structure for such a loop. The multi-scale simulation was performed for 14 ns. The results of the simulation reveal possible degrees of freedom of the protein. The principal motion observed occurred in the head groups, binding to two DNA operon sites, as they absorbed all the stress from the DNA loop. The rest of the protein shows very little motion. An open conformation of the *lac* repressor about the bottom hinge region has been suggested by experiment. Further studies into the investigation of this motion of the protein are being performed.

BTA UNIT: T

TITLE: Conduction Mechanism of the ClC Chloride Channel

KEYWORDS: ion channel, membrane protein, ion conduction, umbrella sampling

AXIS I: 2

AXIS II: 74H 89

INVEST1: Cohen, Jordi
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% BTA $: 2%

% BTA for AIDS $: 0%

ABSTRACT: The ClC family of anion channels is an ancient gene family present in a wide variety of organisms, including animals, plants and bacteria [71]. The ClCs are functional dimers with two independent pores that exhibit voltage-gating and are selective to passage of small anions. A total of nine ClC genes have been identified in mammals (of which eight are present in humans), where they are known to be expressed in many different tissues [72]. Inherited mutations of ClC can cause diseases such as myotonia [73], Bartter's syndrome [74] and Dent's disease [75]. Despite the fact that the x-ray crystallographic structures of two bacterial ClCs, for *S. typhimurium* and *E. coli*, have recently been solved [76, 77], the molecular mechanisms of anion conduction and gating through these channels are currently poorly understood.

Based on data from the first x-ray structure of ClC [76], a 97,000-atom system was built that contains the channel in a solvated membrane environment. To allow ion permeation, an open-gate structure of the pore was modeled from the wild-type structure by displacing the channel's pore-blocking charged residue [77]. Using this simulation system, the conduction pathway of permeant $Cl^-$ ions across the ClC channel was characterized and the precise locations of the ClC pores were established. Furthermore, the potential of mean force for ion translocation was mapped for a pair of ions going through the channel using umbrella sampling, providing the relevant energy barriers needed to understand the conduction mechanism [78]. While the energy required to extract the single central ion from the pore is enormous, by resorting to this two-ion process, the largest free energy barrier for conduction is reduced significantly to 4–5 kcal/mol. It was thus established that the currently available crystal structures represent an closed state of the channel which

can be opened by moving one single residue, in accord with experiments [77, 79, 80], and that at least two simultaneous chloride ions inside each pore are necessary for ion permeation to occur [78].

BTA UNIT: T

TITLE: Calculating Free energy from Non-equilibrium Simulations

KEYWORDS: Potential of mean force, Non-equilibrium simulation, free energy calculation, steered molecular dynamics, Jarzynski's equality, umbrella sampling

AXIS I: 9

AXIS II: 84 89

INVEST1: Park, Sanghyun
DEGREE1: Ph.D.
DEPT1: Physics
NONHOST1:

INVEST2: Khalili-Araghi, Fatemeh
DEGREE2: B.S.
DEPT2: Physics
NONHOST2:

INVEST3: Tajkhorshid, Emad
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% BTA $: 3%

% BTA for AIDS $: 0%

ABSTRACT: Steered molecular dynamics* (SMD) has been widely used to investigate biomolecules in computer simulations [81]. While SMD simulations often lead to qualitative understanding of biological systems, quantitative analysis is a challenging task. The Resource has been working on developing methods to calculate free energy from SMD simulations, which are intrinsically nonequilibrium, whereas free energy is an equilibrium quantity. Jarzynski's equality provides a way to extract equilibrium information from nonequilibrium processes [82].

The Resource has carried out benchmark studies on free energy calculation from SMD simulations [83, 84]. The helix-coil transition of decalanine was used as an exemplary system. The molecule is small enough (104 atoms) to permit systematic

*URL: `http://www.ks.uiuc.edu/Research/smd_imd/`

study, yet complex enough to be considered a prototype of biomolecular systems. In an SMD simulation performed with NAMD [35], the helix-coil transition was induced by stretching the molecule with force. The free energy change involved in the helix-coil transition was calculated by means of Jarzynski's equality. Various averaging schemes were examined and compared to the conventional umbrella sampling method. It was found that the efficiencies of our method and umbrella sampling are comparable [83]. In another study, we have outlined the derivation of Jarzynski's equality, its generalization to isobaric-isothermal processes, and its implications in relation to the second law of thermodynamics and computer simulations. In the relevant regime of steering by means of stiff springs, it is demonstrated that the work on the system is Gaussian-distributed regardless of the speed of the process simulated. In this case, the cumulant expansion of Jarzynski's equality can be safely terminated at second order.

BTA UNIT: C

TITLE: Micelle formation around transmembrane helices

KEYWORDS: helix-helix association, micelle, glycophorin A, molecular dynamics

AXIS I: 2 7a

AXIS II: 74F 74H 77 89

INVEST1: Rosemary Braun
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NONHOST1:

INVEST2: Donald M. Engelman
DEGREE2: Ph.D.
DEPT2: Mol. Biophys. & Biochem.
NONHOST2: Yale

% BTA $: 2%

% BTA for AIDS $: 0%

ABSTRACT: A detailed description of the interaction of protein helices with one another in lipid environments is essential to an understanding of the insertion and formation of membrane proteins, the rupturing of membranes by toxins, the action of antibiotic peptides, and other biological processes. Errors in protein aggregation resulting from mutations have been shown to have serious medical consequences, including fatal cancers [85–87]. Transmembrane helices embedded in micelles provide a small system in which their interaction may be studied. The Resource is carrying out a diverse set of molecular dynamics simulations to elucidate the effect of mutations on the positioning of a helix in a micelle and the effect of mutations on helix association in lipid environments [88].

The transmembrane helix of human glycophorin A (GpA) is known to form a stable homodimer under a variety of conditions and has thus been used for many years as a system by which to study the association of transmembrane helices [89–94]. Molecular dynamics simulations of sodium dodecyl sulfate (SDS) and the GpA dimer provide an atomic-level depiction of the dynamics of micelle aggregation and helix association. Simulations resulting in spontaneous micelle formation about the GpA dimer were carried out, with an configuration consisting of the GpA dime NMR

structure surrounded by water and 58 randomly placed SDS molecules, corresponding to 125 mM SDS concentration. The 65,000 atom system was subject to molecular dynamics simulations lasting 24 ns in the NpT ensemble using NAMD [35]. The long simulation time permitted the observation of the diffusion and organization of SDS molecules into a small micelle comprising 24 SDS molecules around GpA by the end of 19 ns [88]. Deformation of the hydrophobic GpA helices in water is resolved after being partially surrounded by SDS at 9.5 ns [88]. The properties of the spontaneously formed micelle surrounding the GpA were found to be indistinguishable from those of the pre-formed micelle surrounding the GpA dimer and closely resemble experimentally measured parameters [88]. Instabilities were observed in simulation systems where the residues along the GpA helix-helix interface were mutated [88].

BTA UNIT: T

TITLE: Fast Methods for Electrostatics and Polarization

KEYWORDS: fast electrostatic methods, hierarchical interpolation, polarization

AXIS I: 9

AXIS II: 42

INVEST1: Hardy, David J.
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INVEST2: Wang, Wei
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INVEST3: Skeel, Robert
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% BTA $: 3%

% BTA for AIDS $: 0%

ABSTRACT: NAMD [35] uses the particle–mesh–Ewald (PME) method [95] to compute electrostatics for periodic simulations, but it currently lacks a fast algorithm for nonperiodic systems. Work is ongoing to develop a fast electrostatics method based on a hierarchical interpolation of softened pairwise potentials on multiple grids [96, 97]. Tests show that, compared to the fast multipole algorithm, this *multiple grid method*[*] is four times faster when used with error tolerances appropriate for molecular dynamics. This method has also been implemented for Ewald periodic boundary conditions and demonstrated to be competitive with PME. A parallel implementation of the multiple grid method is being developed for the next version of NAMD, to provide fast electrostatics for nonperiodic systems and a more scalable alternative for periodic systems.

[*]URL: `http://www.ks.uiuc.edu/Research/Algorithms/`

There is growing evidence that current force fields are inadequate for many scientific studies. The inclusion of electronic polarizability is the single most desirable improvement [98–100], however, the high computational cost has impeded the development of polarizable force fields. The goal of the second part of this subproject is to reduce the cost of computing polarizability to make it more useful for molecular dynamics. The self-consistent implementation of the point dipole model has been chosen because it is applicable to kinetic as well as thermodynamic calculations and provides a standard against which other approximation approaches can be compared. In previously reported work, a reduction in the cost by a factor of nearly two had been obtained compared to published results [101]. Using a recently published technique [102], another factor of two improvement has now been obtained, reducing the cost of including polarizability to only about twice the cost of computing long range electrostatics. Software will be written and tested using an existing sequential molecular dynamics program so that it will be straightforward to incorporate polarizable force fields into the next version of NAMD.

BTA UNIT: T, D, S

TITLE: BioCoRE: Biological Collaborative Research Environment

KEYWORDS: web-based collaboratory, software engineering, internet, evaluation, collaborative research environment

AXIS I: 9

AXIS II: 42 51 89

INVEST1: Budescu, Gila
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INVEST2: Kalé, Laxmikant V.
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INVEST3: Brunner, Robert
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INVEST4: Vandivort, Kirby
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INVEST5: Bach, Michael
DEGREE5: B. S.
DEPT5: Beckman Institute
NONHOST5:

INVEST6: Brandon, David
DEGREE6: Ph. D.
DEPT6: Speech Communication
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INVEST7: Dagit, Derek

DEGREE7: B. S.

DEPT7: Computer Science

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INVEST8: Koenig, Greg

DEGREE8: M. S.

DEPT8: Computer Science

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INVEST9: Kumar, Sameer

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INVEST10: Potnuru, Mani

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DEPT10: Computer Science

NONHOST10:

% BTA $: 17%

% BTA for AIDS $: 0%

ABSTRACT: BioCoRE [103] is a web-based collaborative environment designed to enhance biomedical research and training. * By using a standard web-browser (on a desktop, laptop computer or handheld PDA) scientists create projects in which all private data is secure and is shared only within each project. Researchers use BioCoRE to create input files for supercomputer runs, submit jobs to remote sites including supercomputers, and share the visualization of molecular systems across distances. BioCoRE features a synchronous and asynchronous chat, a project-wide "bookmarks" file for sharing web links, as well as a web-based filesystem. Summary pages within BioCoRE inform the project team of the project status. BioCoRE sessions are recorded and can be reviewed by all project team members. A built-in evaluation component provides systematic and continuous user feedback.

Major BioCoRE developments in the past year include a redesign of the interface as well as an improved VMD synchronization tool.

*URL: `http://www.ks.uiuc.edu/Research/biocore/`

Other improvements and additions include support for the newest supercomputers including NCSA's Teragrid machine. The notebook area now has the capability to send messages via email to members, which helps integrate BioCoRE into their workflow. As a result of the demands placed on BioCoRE by the large number of students simultaneously accessing it during the Summer School (see p. 14), the Resource implemented scalability improvements, particularly in the perceived speed of the Control Panel. Several of these changes were incorporated and put to use before the end of the school.

Future BioCoRE efforts will focus on additional integration of biomedical applications (partially via increased capabilities of the Application Programming Interface), further development of the training arena, and on increased adoption of BioCoRE by the community.

BTA UNIT: T,S

TITLE: VMD: High Performance, Low Cost Molecular Visualization

KEYWORDS: molecular visualization, interactive simulation

AXIS I: 9

AXIS II: 42 89

INVEST1: Stone, John E
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INVEST2: Caddigan, Eamon
DEGREE2: B.S.
DEPT2: Computer Engineering
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% BTA $: 11%

% BTA for AIDS $: 0%

ABSTRACT: VMD [104] is a molecular visualization program that provides interactive biomolecular display and analysis capabilities. VMD incorporates built-in scripting features for user extensibility and automation of complex visualization and analysis.*

VMD runs on all major operating systems and supports computers ranging from laptops to graphics supercomputers, allowing it to scale with varying problem size. VMD utilizes advanced hardware technologies including 3-D graphics accelerators, stereoscopic displays, six-degree-of-freedom input devices with haptic feedback, cluster-based rendering systems, and 64-bit processors.

In the past year, VMD has been ported to the new 64-bit AMD Athlon64, Opteron, and Intel IA-32E processors, providing support for very large data sets crucial to analysis of cutting-edge molecular dynamics simulations. Significant improvements have been made to the speed and quality of interactive molecular rendering in VMD, particularly for isosurfaces extracted from potential maps, electron density maps, and other volumetric data sets. New graphical representation options provide an easy method for viewing the superposition of multiple timesteps in molecular dynamics trajectories. With these features, researchers may visualize the motions of

*URL: `http://www.ks.uiuc.edu/Research/vmd/`

key components of biomolecules as they undergo structural transitions. Improvements in the use of external rendering packages such as Tachyon and POV-Ray allow the production of higher quality images, particularly those containing solvent-accessible surfaces with detailed coloring. Several new plugins have been developed in the past year, including an improved "solvate" plugin which aids in preparing molecular dynamics simulations, a new electrostatics plugin linked to the APBS (Adaptive Poisson-Boltzmann Solver) package, and support for several new molecular and volumetric file formats.

VMD 1.8.2 was released in December 2003. More than 8,100 unique users have registered and downloaded VMD 1.8.2, over 1,600 of whom are NIH-funded researchers. The next planned release of VMD, version 1.8.3, is expected to be released by August 2004.

BTA UNIT: T, S

TITLE: NAMD: Scalable Molecular Dynamics Software

KEYWORDS: molecular dynamics simulation, modeling, parallel computation, object-oriented programming, message-driven programming

AXIS I: 9

AXIS II: 42 89

INVEST1: Phillips, James
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INVEST2: Skeel, Robert
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DEPT2: Beckman Institute
NONHOST2:

INVEST3: Kale, Laxmikant
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INVEST4: DeSouza, Jay
DEGREE4: M.S.
DEPT4: Computer Science
NONHOST4:

INVEST5: Kumar, Sameer
DEGREE5: M.S.
DEPT5: Computer Science
NONHOST5:

INVEST6: Zheng, Gengbin
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DEPT6: Computer Science
NONHOST6:

% BTA $: 15%

% BTA for AIDS $: 0%

ABSTRACT: NAMD* is a parallel molecular dynamics code designed for high performance simulation of large biomolecular systems [35]. NAMD employs the prioritized message-driven execution capabilities of the Charm++/Converse parallel runtime system,† allowing excellent parallel scaling on both massively parallel supercomputers and commodity workstation clusters. NAMD is distributed free of charge to over 9000 registered users as both source code and convenient precompiled binaries.

NAMD 2.5 was released in September 2003 and has been downloaded by over 2600 users, 500 of whom are NIH-funded. This release features the load balancer and communication library improvements from the *2002 Gordon Bell Award* [105] effort for improved scaling on large parallel machines. For more modest Linux clusters we provide versions based on TCP rather than UDP networking, with improved performance on gigabit ethernet, and all released Linux binaries are built with the Intel compiler for better performance on Pentium 4 and Xeon processors and no penalty for Pentium III or Athlon processors. The incorporation of automatically adjusted pairlists into NAMD's electrostatic and van der Waals interaction routines has resulted in up to a 50% serial performance increase. New functionality includes the ability to read trajectory files to analyze interaction energies and improved constant pressure simulation methods.

NAMD has been ported to a pair of significant new Linux clusters at the National Center for Supercomputing Applications (NCSA). First, the NCSA TeraGrid cluster, for which NAMD was a flagship application, provides 512 Itanium 2 processors and will soon be expanded with over 600 more. Second, the NCSA Tungsten cluster, the fourth-fastest supercomputer in the world, provides 2900 Xeon processors. NAMD has also been ported to the new AMD64 architecture, providing a 13% performance boost for Opteron processors and preparing NAMD for the "Red Storm" system recently ordered by the Pittsburgh Supercomputing Center. NAMD 2.6, which will support these new platforms, will be released in June 2004.

*URL: `http://www.ks.uiuc.edu/Research/namd/`

†URL: `http://charm.cs.uiuc.edu/`

BTA UNIT: T, S, D

TITLE: Computational Facility

KEYWORDS: parallel computing, visualization, network

AXIS I: 11

AXIS II: 42 89

INVEST1: Tim Skirvin

DEGREE1: B.S.

DEPT1: Beckman Institute

NONHOST1:

% BTA $: 17%

% BTA for AIDS $: 0%

ABSTRACT: The last year has seen the Resource consolidate its computational facility* onto modern hardware. We have upgraded our facility in four main categories: the local Linux clusters, the local visualization workstations, desktop workstations and laptops, and infrastructure. These changes have allowed us to better manage and support our 50 local and 69 remote users while continuing to increase our capacity to simulate and analyze ever-larger molecular systems cost-effectively.

In June 2004 the Resource has upgraded its local compute clusters with the purchase of three additional 48-processor Intel Xeon clusters†. These new clusters, utilizing space-efficient rack-mount systems, double our local computational capacity while still leaving room for future expansion. The new machines are managed through the same open-source Clustermatic package as our existing clusters, which will ensure maximum system utilization and manageability while maintaining our current flexibility.

Keeping pace with our local compute upgrades, our total supercomputer time‡, 1.9 million Service Units across three major supercomputer centers (PSC's LeMieux, NCSA's Xeon cluster, and the national Teragrid), represents a 30% increase in raw CPU time. Scaled to match the increases in processing speeds, this represents a 40% increase in our available supercomputing power.

*URL: `http://www.ks.uiuc.edu/Development/Computers/`

†URL: `http://www.ks.uiuc.edu/Development/Computers/Clusters/ariel.html`

‡URL: `http://www.ks.uiuc.edu/Development/Computers/nrac.html`

The most significant upgrade to the Resource's graphical capacity in the last year was the acquisition of a SunFire V880z visualization server. This system, which is undergoing testing in our local environment before being deployed in our 3D visualization facility, offers unmatched graphics and computational power. This system contains two XVR-4000 video boards, each with over a gigabyte of texture memory; their anti-aliasing capabilities offer the best possible visual image, and is powerful enough to let us work with large volumetric data sets such as electron density maps, electron orbitals, and time-varying spatial occupancy grids. As the Resource also helped test these boards, they are essentially custom-designed for our research. The system also has 32 gigabytes of memory, allowing us to simulate and analyze systems significantly (8x) larger and more complex than any of our existing machines have allowed to date.

Having consolidated virtually all researcher desktops onto PCs running Linux, we have spent much of the year focusing on usability improvements for researcher workstations. Our researchers have had their CRT monitors replaced with LCD flat-panels, offering significant additional desk space and ergonomic benefit. We have installed Crossover Office on all of our Linux systems, giving access to Microsoft documents while maintaining the convenience, security, and maintainability of a Unix environment. Finally, we have added 31 laptops to the environment, bringing the total up to 46, allowing users to continue their work while on the road or from home; 20 of these laptops are reserved for training in hands-on workshops.

To match the above improvements in computational and graphics power, the past year has seen a significant modernization of our computer infrastructure. On the network side, the Beckman Institute has upgraded our switches to Gigabit Ethernet, improving network capacity and performance by a factor of 10. Server-wise, we have replaced our aging Sun Ultra 5 systems with SunFire V100s and V210s, improving stability dramatically. All of our files are now served from SunFire 280R servers, sharing a total of nearly 10 TB of data, more than double that of last year; 4.5 TB of this is backed up nightly using SuperDLT tape drives and in-house software. These upgrades have given us the resources to store and efficiently analyze our large molecular simulations.

# Resource Summary

# Resource Summary (2003–2004)

| | T | C | S | D | TOT |
|---|---|---|---|---|---|
| Number of publications | 28 | 25 | 24* | 6 | 83 |
| Number of subprojects | 9 | 7 | 4 | 2 | 15** |
| Number of investigators | 30 | 32 | 17 | 12 | 59*** |
| Percent of BTA funds allocated | 39% | 25% | 24% | 12% | 100% |
| Percent of BTA funds allocated for AIDS | 0% | 0% | 0% | 0% | 0% |
| Service Fees Collected | 0 | 0 | 0 | 0 | 0 |
| Other funds ($) | $190,000 | $170,000 | $0 | $70,000 | $430,000 |

**T**: Technological research and development

**C**: Collaborative research

**S**: Service

**D**: Dissemination and training

*Software releases.

**Subprojects belonging in more than one BTA unit are counted more than once.

***Investigators contributing in more than one BTA unit are counted more than once.

# Geographical Data (2003–2004)

| State or Country | Number of Investigators |
|---|---|
| IL | 38 |
| WI | 1 |
| UT | 2 |
| TX | 1 |
| NY | 2 |
| NC | 1 |
| MA | 1 |
| MO | 2 |
| MD | 1 |
| CT | 1 |
| CA | 1 |
| AZ | 1 |
| Japan | 1 |
| Germany | 1 |
| France | 1 |
| England | 1 |
| Denmark | 1 |
| Canada | 2 |
| Total | 59 |

# BTA Unit T (2003–2004)

| Investigator | Non-Host Institution (Principal Investigator) | Sources of Support | |
|---|---|---|---|
| | | TYPE | AGENCY |
| Bach, Michael | | FED | NIH |
| Balaeff, Alexander | IBM | IND | |
| Brandon, David | | FED | NIH |
| Brunner, Robert | | FED | NIH |
| Budescu, Gila | | NIH | NIH |
| Caddigan, Eamon | | FED | NIH |
| Cohen, Jordi | | FED | NIH |
| Dagit, Derek | | FED | NIH |
| DeSouza, Jay | | FED | NIH |
| Grayson, Paul | | OTH | |
| Hardy, David J. | | FED | NIH |
| Jensen, Morten | Tech U of Denmark Copenhagen, Denmark | OTH | |
| Kale, Laxmikant | | FED | NIH |
| Khalili-Araghi, F. | | FED | NIH |
| Koenig, Greg | | FED | NIH |
| Kumar, Sameer | | FED | NIH |
| Mahadevan, L. | Harvard U (Mahadevan) | OTH | |
| Park, Sanghyun | | FED | NIH |
| Phillips, James | | FED | NIH |
| Potnuru, Mani | | FED | NIH |
| Skeel, Robert | | FED | NIH |
| Skirvin, Tim | | FED | NIH |
| Stone, John E | | FED | NIH |
| Tajkhorshid, Emad | | FED | NIH |
| Vandivort, Kirby | | FED | NIH |
| Villa, Elizabeth | | FED | NIH |
| Wang, Wei | | FED | NIH |
| Yu, Jin | | FED | NSF |

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*continued from previous page*

| Investigator | Non-Host Institution (Principal Investigator) | Sources of Support | |
|---|---|---|---|
| | | **TYPE** | **AGENCY** |
| Zheng, Gengbin | | FED | NIH |
| Zhu, Fangqiang | | FED | NIH |

# BTA Unit C (2003–2004)

| Investigator | Non-Host Institution (Principal Investigator) | Sources of Support | |
|---|---|---|---|
| | | TYPE | AGENCY |
| Aksimentiev, Aleksei | | FED | NSF |
| Balabin, Ilya | | FED | NSF |
| Balaeff, Alexander | IBM | IND | |
| Braun, Rosemary | | FED | NIH |
| Campbell, Iain | Oxford U, UK (Campbell) | OTH | |
| Chakrabarti, Nilmadhab | Hospital for Sick Children Toronot, Canada (Pomes) | OTH | |
| Chu-Cruz, Eduardo | | FED | NSF |
| Craig, David | Washington U (Vogel) | OTH | |
| Damjanović, Ana | Johns Hopkins U | OTH | |
| Dittrich, Markus | | FED | NSF |
| Engleman, Donald M. | Yale U (Engelman) | FED | NIH |
| Fillingame, Robert | U Wisconsin Madison (Fillingame) | OTH | |
| Fromme, Petra | Arizona State U (Fromme) | OTH | |
| Gao, Mu | | FED | NIH |
| Hayashi, Shigehiko | Kyoto U, Japan (Hayashi) | OTH | |
| Ilan, Boaz | U Utah (Voth) | OTH | |
| Israelewitz, Barry | | FED | NIH |
| Kanchanawarin, C. | | FED | NIH |
| Kleinekathöfer, U. | Tech U Chemnitz Germany | OTH | |
| Leburton, Jean-Pierre | (Leburton) | FED | NSF |

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| Investigator | Non-Host Institution (Principal Investigator) | Sources of Support | |
|---|---|---|---|
| | | TYPE | AGENCY |
| Lequin, Olivier | U Pierre et Marie Curie Paris, France (Lequin) | OTH | |
| Lu, Deyu | | FED | NIH |
| Mahadevan, L. | Cambridge U, UK (Mahadevan) | OTH | |
| Pomes, Regis | Hospital for Sick Children Toronot, Canada (Pomes) | OTH | |
| Ritz, Thorsten | UC Irvine (Ritz) | OTH | |
| Roux, Benoit | Cornell (Roux) | FED | NIH |
| Sener, Melih | | FED | NSF |
| Timp, Gregory | (Timp) | FED | NSF |
| Villa, Elizabeth | | FED | NIH |
| Vogel, Viola | Washington U (Vogel) | FED | NIH |
| Voth, Gregory | U Utah (Voth) | OTH | |
| Weber, Joachim | Texas Tech U (Weber) | OTH | |

# BTA Unit S (2003–2004)

| Investigator | Non-Host Institution (Principal Investigator) | Sources of Support | |
|---|---|---|---|
| | | TYPE | AGENCY |
| Bach, Michael | | FED | NIH |
| Brandon, David | | FED | NIH |
| Brunner, Robert | | FED | NIH |
| Budescu, Gila | | FED | NIH |
| Caddigan, Eamon | | FED | NIH |
| Dagit, Derek | | FED | NIH |
| DeSouza, Jay | | FED | NIH |
| Kale, Laxmikant | | FED | NIH |
| Koenig, Greg | | FED | NIH |
| Kumar, Sameer | | FED | NIH |
| Phillips, James | | FED | NIH |
| Potnuru, Mani | | FED | NIH |
| Skeel, Robert | | FED | NIH |
| Skirvin, Tim | | FED | NIH |
| Stone, John E | | FED | NIH |
| Vandivort, Kirby | | FED | NIH |
| Zheng, Gengbin | | FED | NIH |

# BTA Unit D (2003–2004)

| Investigator | Non-Host Institution (Principal Investigator) | Sources of Support | |
|---|---|---|---|
| | | TYPE | AGENCY |
| Bach, Michael | | FED | NIH |
| Brandon, David | | FED | NIH |
| Brunner, Robert | | FED | NIH |
| Budescu, Gila | | FED | NIH |
| Dagit, Derek | | FED | NIH |
| Kale, Laxmikant | | FED | NIH |
| Koenig, Greg | | FED | NIH |
| Kumar, Sameer | | FED | NIH |
| Potnuru, Mani | | FED | NIH |
| Skirvin, Tim | | FED | NIH |
| Vandivort, Kirby | | FED | NIH |

BTA unit: ( T )

NUMBER PUBLISHED -

Books: **0** Papers: **19** Abstracts: **9**

NUMBER IN PRESS -

Books: **0** Papers: **0** Abstracts: **0**

PUBLISHED:

**Books:**
None.

**Papers:**

- Cohen J, & Schulten K. Mechanism of anionic conduction across ClC. *Biophysical Journal,* 86:836-845, 2004.*****
- DeSouza J, & Kale LV. Jade: A Parallel Message-Driven Java. *Proceedings of the 2003 Workshop on Java in Computational Science,* held in conjunction with the *International Conference on Computational Science (ICCS 2003),* Melbourne, Australia, and Saint Petersburg, Russian Federation. June 2-4, 2003.*****
- Dittrich M, Hayashi S, & Schulten K. On the mechanism of ATP hydrolysis in F1-ATPase. *Biophysical Journal,* 85:2253-2266, 2003.*****
- Grayson P, Tajkhorshid E, & Schulten K. Mechanisms of selectivity in channels and enzymes studied with interactive molecular dynamics. *Biophysical Journal,* 85:36-48, 2003.*****
- Gullingsrud J, & Schulten K. Gating of MscL studied by steered molecular dynamics. *Biophysical Journal,* 85:2087-2099, 2003.*****
- Gullingsrud J, & Schulten K. Lipid bilayer pressure profiles and mechanosensitive channel gating. *Biophysical Journal,* 86:3496 to 3509, 2004.*****
- Hayashi S, Tajkhorshid E, & Schulten K. Molecular dynamics simulation of bacteriorhodopsin's photoisomerization using ab initio forces for the excited chromophore. *Biophysical Journal,* 85:1440-1449, 2003.*****
- Kale LV, Kumar S, Zheng G, Lee CW. Scaling Molecular Dynamics to 3000 Processors with Projections: A Performance Analysis Case Study, *Proceedings of Terascale Performance Analysis Workshop, International Conference on Computational Science(ICCS)*, Melbourne, Australia, and Saint Petersburg, Russian Federation. June 2-4, 2003.*****

- Kumar S, & Kale LV. Opportunities and Challenges of Modern Communication Architectures: Case Study with QsNet, In *Proceedings of the CAC Workshop at IPDPS'04,* Santa Fe, NM, April, 2004.*

- Lu D, Grayson P, & Schulten K. Glycerol conductance and physical asymmetry of the *Escherichia coli* glycerol facilitator GlpF. *Biophysical Journal,* 85:2977-2987, 2003.*

- Ma Q, Izaguirre J, & Skeel RD, Nonlinear instability in multiple time-stepping molecular dynamics. *Proceedings of the 18th ACM Symposium on Applied Computing (SAC'03)*, 167-17, 2003.*

- Ma Q, Izaguirre J, & Skeel RD, Verlet-I/r-RESPA is limited by nonlinear instability. *SIAM J. Sci. Comput. 24*, 1951-1973, 2003.*

- Park S, Khalili-Araghi F, Tajkhorshid E, & Schulten K. Free energy calculation from steered molecular dynamics simulations using Jarzynski's equality. *Journal of Chemical Physics,* 119:3559-3566, 2003.*

- Park S, & Schulten K. Calculating potentials of mean force from steered molecular dynamics simulations. *Journal of Chemical Physics,* 120:5946-5961, 2004.*

- Park S, Sener MK, Lu D, & Schulten K. Reaction paths based on mean first-passage times. *Journal of Chemical Physics,* 119:1313-1319, 2003.*

- Zheng G, Kakulapati G, & Kale LV. BigSim: A Parallel Simulator for Performance Prediction of Extremely Large Parallel Machines, In *Proceedings of the IPDPS'04,* Santa Fe, NM, April, 2004.*

- Zheng G, Wilmarth T, Lawlor OS, Kale LV, Adve S, Padua D, & Guebelle G. Performance Modeling and Programming Environments for Petaflops Computers and the Blue Gene Machine, In *Proceedings of the IPDPS'04,* Santa Fe, NM, April, 2004.*

- Zhu F, & Schulten K. Water and proton conduction through carbon nanotubes as models for biological channels. *Biophysical Journal,* 85:236-244, 2003.*

- Zhu F, Tajkhorshid E, & Schulten K. Theory and simulation of water permeation in aquaporin-1. *Biophysical Journal,* 86:50-57, 2004.*

**Abstracts:**

- Aksimentiev A, Schulten K, Heng J, Ho C, & Timp G. Molecular dynamics simulations of a nanopore device for DNA sequencing. BIOPHYS J 86 (1): 480A-480A Part 2 Suppl. S JAN 2004.

- Braun R, & Schulten K. Molecular dynamics studies of sodium dodecyl sulfate aggregation about glycophorin-A transmembrane domain. BIOPHYS J 86 (1): 560A-560A Part 2 Suppl. S JAN 2004.

- Cohen J, & Schulten K. Mechanism of anionic permeation across ClC. BIOPHYS J 86 (1): 5A-5A Part 2 Suppl. S JAN 2004.

- Dittrich M, Hayashi S, & Schulten K. QM/MM study of ATP hydrolysis in F-1 ATPase. BIOPHYS J 86 (1): 246A-246A Part 2 Suppl. S JAN 2004.

- Gullingsrud J, & Schulten K. Lipid bilayer pressure profiles and mechanosensitive channel gating. BIOPHYS J 86 (1): 547A-547A Part 2 Suppl. S JAN 2004.

- Isralewitz B, Tajkhorshid E, & Schulten K. Conformation change during simulated rotation of F-1-ATPase central stalk. BIOPHYS J 86 (1): 245A-245A Part 2 Suppl. S JAN 2004.

- Sotomayor M, & Schulten K. Molecular dynamics study of gating in the mechanosensitive channel of small conductance MscS. BIOPHYS J 86 (1): 546A-546A Part 2 Suppl. S JAN 2004.

- Villa E, Balaeff A, & Schulten K. Lac repressor-DNA loop dynamics. BIOPHYS J 86 (1): 591A-592A Part 2 Suppl. S JAN 2004.

- Zhu F, Tajkhorshid E, & Schulten K. Theory and simulation of water permeation in single-file water channels. BIOPHYS J 86 (1): 256A-256A Part 2 Suppl. S JAN 2004.

IN PRESS:

**Books:**
None.

**Papers:**
None.

**Abstracts:**
None.

BTA unit: ( C )

NUMBER PUBLISHED -

Books: **0** Papers: **11** Abstracts: **7**

NUMBER IN PRESS -

Books: **0** Papers: **7** Abstracts: **0**

PUBLISHED:

**Books:**
None

**Papers:**


- Aksimentiev A, Balabin IA, Fillingame RH, & Schulten K. Insights into the molecular mechanism of rotation in the Fo sector of ATP synthase. *Biophysical Journal,* 86:1332-1344, 2004.*
- Amaro R, Tajkhorshid E, & Luthey-Schulten L. Developing an Energy Landscape for the Novel Function of a $(\alpha/\beta)_8$ Barrel: Ammonia Conduction through HisF. *Proceedings of the National Academy of Sciences, USA,* 100:7599-7604, 2003.*
- Balaeff A, Mahadevan L, & Schulten K. Structural basis for cooperative DNA binding by CAP and Lac repressor. *Structure,* 12:123-132, 2004.*
- Chakrabarti N, Tajkhorshid E, Roux B, & Pomes R. Molecular basis of proton blockage in aquaporins. *Structure,* 12, 65-74, 2004.*
- Craig D, Gao M, Schulten K, & Vogel V. Tuning the mechanical stability of fibronectin type III modules through sequence variation. *Structure,* 12:21-30, 2004.*
- Gao M, Craig D, Lequin O, Campbell I D, Vogel V, & Schulten K. Structure and functional significance of mechanically unfolded fibronectin type III1 intermediates. *Proceedings of the National Academy of Sciences, USA,* 100:14784-14789, 2003.*
- Ilan B, Tajkhorshid E, Schulten K, & Voth GA. The mechanism of proton exclusion in aquaporin channels. *PROTEINS: Structure, Function, and Bioinformatics,* 55:223-228, 2004.*
- Sarikaya M, Tamerler C, Jen AK-Y, Schulten K, & Baneyx FM. Molecular biomimetics: nanotechnology through biology. *Nature Materials,* 2:577-585, 2003.
- Siebert H-C, Andre S, Lu S-Y, Frank M, Kaltner H, van Kuik JA, Korchagina EY, Bovin N, Tajkhorshid E, Kaptein R, Vliegenhart JFG, von der Lieth C-W,

Jimenez-Barbero J, Kopitz J, & Gabius H-J . Unique Conformer Selection of the Human Growth-regulatory Lectin Galectin-1 for Ganglioside GM1 Versus Bacterial Toxins. *Biochemistry* 42:14762-14773, 2003.

- Bayas MV, Schulten K, & Leckband D. Forced dissociation of the strand dimer interface between C-cadherin ectodomains. *Mechanics and Chemistry of Biosystems* 1:101-111, 2004.*

- Sener MK, Park S, Lu D, Damjanovic A, Ritz T, Fromme P, & Schulten K. Excitation migration in trimeric cyanobacterial photosystem I. *Journal of Chemical Physics* 120:11183-11195, 2004. *

**Abstracts:**

- Aksimentiev A, Balabin I, Fillingame RH, Schulten K. Molecular mechanism of energy conversion in Fo ATP synthase. BIOPHYS J 86 (1): 245A-245A Part 2 Suppl. S JAN 2004

- Ho C, Heng JB, Timp R, Aksimentiev O, Schulten K, Shaw A, Sligar S, Twesten R, Wen JG, Timp G. Molecular sensing using silicon nanopores. BIOPHYS J 86 (1): 481A-481A Part 2 Suppl. S JAN 2004

- Ilan B, Tajkhorshid E, Schulten K, Voth GA. The mechanism of proton exclusion in aquaporin channels. BIOPHYS J 86 (1): 131A-131A Part 2 Suppl. S JAN 2004

- Khalili-Araghi F, Isgro TA, Sotomayor M, Villa E, Schulten K. Mechanical properties of ubiquitin chains. BIOPHYS J 86 (1): 411A-412A Part 2 Suppl. S JAN 2004

- Kleinekathoefer U, Isralewitz B, Dittrich M, Schulten K. Molecular dynamics simulations of isolated beta-subunits of F-1-ATPase. BIOPHYS J 86 (1): 246A-246A Part 2 Suppl. S JAN 2004

- Meyer GR, Gullingsrud J, Martinac B, Schulten K. Molecular dynamics studies of bilayer deformation forces on MscL structure. BIOPHYS J 86 (1): 546A-546A Part 2 Suppl. S JAN 2004

- Tajkhorshid E, Jensen M, & Schulten K. Electrostatics regulation of substrate permeation and selectivity of aquaporins. BIOPHYS J 86 (1): 5A-5A Part 2 Suppl. S JAN 2004

IN PRESS:

**Books:**
None

**Papers:**

- Autenrieth F, Tajkhorshid E, Baudry J, & Luthey-Schulten Z. Classical force field parameters for the heme prosthetic group of cytochrome c. *Journal of Computational Chemistry.* 2004. In press.*
- Balaeff A, Koudella CR, Mahadevan L, & Schulten K. Modeling DNA loops using continuum and statistical mechanics. *Philosophical Transactions of the Royal Society of London A. (Mathematical, Physical and Engineering Sciences),* 2004. In press.*
- Braun R, Engelman DM, & Schulten K. Molecular dynamics simulations of micelle formation around dimeric glycophorin A transmembrane helices. *Biophysical Journal,* 2004. In press.*
- Larios E, Li JS, Schulten K, Kihara H, & Gruebele M. Multiple probes reveal a native-like intermediate during the low-temperature refolding of ubiquitin. *Journal of Molecular Biology,* 2004. In press.*
- Larios E, Yang WY, Schulten K, & Gruebele M. A similarity measure for partially folded proteins: application to unfolded and native-like conformational fluctuations. *Chemical Physics,* 2004. In press.*
- Li Y, Lu D, Rotkin SV, Schulten K, & Ravaioli U. Electronic structure and dielectric behavior of finite-length single-walled carbon nanotubes. In Proceedings of the Fourth IEEE Conference on Nanotechnology, Munich, Germany, 2004. In press.*
- Villa E, Balaeff A, Mahadevan L, & Schulten K. Multi-scale method for simulating protein-DNA complexes. *Multiscale Modeling and Simulation,* 2004. In press.*

**Abstracts:**
None

BTA unit: ( S )

NUMBER PUBLISHED -

Books: **0** Papers: **0** Abstracts: **0**

NUMBER IN PRESS -

Books: **0** Papers: **0** Abstracts: **0**

PUBLISHED:

**Books:**
None.

**Papers:**
None.

**Abstracts:**
None.

IN PRESS:

**Books:**
None.

**Papers:**
None.

**Abstracts:**
None.

**Software Releases (2003-2004)**

- VMD: 1.8.3 approaching beta; 1.8.2 released December 2003
- NAMD: 2.6 expected June 2004; 2.5 released September 2003
- BioCoRE: Beta version of next generation environment May 2004; Incremental updates every few weeks*
- MDTools: released 17 new software packages since October 2003, and updated two. A full list:
  - DBIx::Frame - An extension of Perl DBI which a framework with better logging, and standardized interfaces to common operations. The basic framework for the below databases. (updated, Oct 2003)

*URL:`http://www.ks.uiuc.edu/Research/biocore/announce/changeLog.shtml`

    * TCB::Publications - a publications database, based on DBIx::Frame. (May 2004)
    * TCB::Seminar - a seminar database, based on DBIx::Frame. (May 2004)
    * TCB::System - A sysadmin database, based on DBIx::Frame. Uses the following sub-packages: (May 2004)
        · TCB::Equipment - Equipment and Software. (May 2004)
        · TCB::Loan - Equipment Loans. (May 2004)
        · TCB::Help - Help Database. (May 2004)
        · TCB::SysLoads - System Loads and Supercomputers. (May 2004)
        · TCB::PortMap - Port Map. (May 2004)
        · TCB::System::Obsolete - Obsolete Tables. (May 2004)
    * TCB::Library - a book library database, based on DBIx::Frame. (Oct 2003)
    * TCB::AddressBook - a basic address book, based on DBIx::Frame. (updated, May 2004)
    * TCB::mysql - DBIx::Frame access the MySQL authentication database. (May 2004)
    * TCB::Conference - conference registration with DBIx::Frame. (May 2004)
  – TapeChanger::MTX - Perl module to control tape changers, using the MTX package. (Jan 2004)
  – TCB::Internal - Perl module for performing TCB web page layouts. (May 2004)
  – TCB::AddUser - Perl module for adding and managing users (May 2004)
  – CGI::SHTML - Perl module for parsing Server-Side Includes. (May 2004)
  – HTML::FormRemove - Perl module for removing form tags from HTML. (May 2004)

BTA unit: ( D )

Total for last year (2003-2004)

NUMBER PUBLISHED -

Books: **2** Papers: **1** Abstracts: **0**

NUMBER IN PRESS -

Books: **1** Papers: **2** Abstracts: **0**

PUBLISHED:

**Books:**

- Tajkhorshid E, Aksimentiev A, Balabin I, Gao M, Isralewitz B, Phillips JC, Zhu F, & Schulten K. Large scale simulation of protein mechanics and function. In Frederic M. Richards, David S. Eisenberg, and John Kuriyan, editors, *Advances in Protein Chemistry,* volume 66, pp. 195-247. Elsevier Academic Press, New York, 2003.*****

**Papers:**

- Aksimentiev A, & Schulten K. Extending the molecular modeling methodology to study insertion of membrane nanopores. *Proceedings of the National Academy of Sciences, USA,* 101:4337-4338, 2004.*****

**Abstracts:**
None.

IN PRESS:

**Books:**

- Sener M, & Schulten K. Physical principles of efficient excitation transfer in light harvesting. In David L. Andrews, editor, *Energy Harvesting Materials.* World Scientific, Singapore, 2004. In press.*****
- Tajkhorshid E, Zhu F, & Schulten K. Kinetic theory and simulation of single-channel water transport. In Ed Sip, editor, *Encyclopedia of Materials Modeling, Vol. 1: Fundamental Models and Methods.* MIT, 2004. In press.*****

**Papers:**

- Baudry J, Tajkhorshid E, & Schulten K. Complementarities and convergence of results in bacteriorhodopsin trimer simulations. *Biophysical Journal,* 2004. In press.*

- Roux B, & Schulten K. Computational Studies of Membrane Channels. *Structure*, 2004. In press.*

**Abstracts:**
None.

**Year 14 Advisory Committee**

The Resource advisory board last (Year 14) met on September 18, 2003, and produced the following report. The Advisory Committee was composed of the following members:

- Dave Thirumalai (chair), U. of Maryland, Theoretical Chemistry
- Angela Gronenborn, NIH, Structural Biology of Proteins and Nucleic Acids
- Mark Lundstrom, Purdue, Electrical and Computer Engineering
- Richard Pastor, NIH/FDA, Theoretical Biophysics
- Mary Schuler, UIUC, Cell and Structural Biology and Plant Biology
- Marc Snir, UIUC, Computer Science

**Report of Year 14 Advisory Committee**

**Advisory Board Report, Sept. 18, 2003**

*NIH Resource for Macromolecular Modelling and Bioinformatics*

**Key Issues:**

The NIH Resource is currently making outstanding contributions in all aspects of its operation. Two ensure that it continues to do so, two key issues must be addressed immediately. In addition, we have identified three important issues that should be addressed in order to ensure the longer term viability and growth of the Resource. A plan to address these issues should be developed as soon as possible.

1) The Resource has an urgent need to enhance its computational power. The PI has secured funds to acquire the requisite computers. However, physical space is not available to house the new hardware cluster. This space requirement is an urgent need that has to be immediately met. Since visualization is such an important part of the resource's activity we strongly recommend that space for graphic facilities is also made available. It is desirable to also make office space available to accommodate short- and long term visitors/collaborators.

2) Dr. Gila Budescu, the senior administrator has recently moved. Administrative support is essential, and we recommend that the Beckman Institute provide resources to replace Dr. Budescu. Additional support is required for 2-3 programmers for continued development of VMD and NAMD, both of which are the major lifelines of the resource. It may be possible for the PI to acquire such support from NIH supplemental funds; if not, university support will be necessary.

3) We feel strongly that it is necessary to relieve the PI, Prof. Klaus Schulten from some of his university commitments (reduction in teaching for example). The responsibilities of the PI are increasing, a natural outcome of the great success of this resource. The continued success of the resource can be assured if the PI's responsibilities in directing this major NIH Resource are reflected in his other university responsibilities.

4) Licensing and commercialization are critical issues for the Resource, and problems are impeding the work of the Resource. The director of the Beckman Center has been made aware of this problem, and we urge him to use his position to help resolve the issues.

5) The committee commends Prof. Klaus Schulten for his exemplary leadership of this major effort that has produced top science and widely used infrastructure. However, the committee is worried that too much of the Resource's activities lie on the shoulders of Prof. Schulten. While the co-PIs play important special roles, their direct contributions seem varied in impact and scope. Additionally, none has general expertise in molecular dynamics of biological systems or appear deeply involved in the management of the Resource. A long-term plan should be developed that would broaden the leadership of the Resource to breed a potential successor to Klaus. We propose that the PI formalizes such a plan, including a mechanism for evaluating the ongoing contributions of current co-PIs and the potential contribution of new co-PIs to the mission of the Resource. We recommend that the director identify and recommend to the committee potential new co-PI's who will be committed to the core mission of the Resource. The plan for evaluating on-going contributions of co-PI's and to identify key new PI's should be provided to the Advisory committee in time for the next meeting. In this manner channeling of resources to new areas could be planned and implemented.

**I. Progress Report**

- VMD Progress

  The last VMD release has expanded platform support, with a port to MacOS X, and has added several useful features. The evolution of VMD toward greater modularity, with a good plugin architecture, will facilitate support to new data formats and integration with various modeling tools.

- NAMD Progress

  The NAMD team won the prestigious Gordon Bell Award given to Resource personnel at the SC2002 conference, recognizing the ability of NAMD to employ over 1000 processors for large scientifically relevant simulations. This is a clear recognition of the importance of NAMD, as a code that both exhibits very good scalability and that is widely used in support of important research by a broad community. New tutorials aimed at users with no molecular modeling experience have been developed to better support and expand the NAMD user community.

- BioCoRE

  BioCoRE is a portal for access to the Resource hardware and software, and a collaborative environment for the users of these resources. Functionality is being added to support better collaboration, integration with the grid and more tools and applications.

  The large number of VMD and NAMD users, including the large number of "repeat customers", clearly indicates that these two software packages are highly successful and broadly used. BioCoRE is a younger project and the number of users is sill in the low hundreds.

- Computer Science

  Professor Skeel described progress on three projects aimed for NAMD3. First was the implementation of a method for assessing numerical artifacts and program bugs by monitoring so-called shadow energy. Second was a "muliple grid" fast electrostatics method that is four times faster than the fast mulipole method previously used by NAMD for nonperiodic boundaries and is comparable to PME for periodic boundaries. The third project concerned faster methods for the self-consistent dipole model for polarizable force fields. It was reported that the use of better methods reduces the extra cost of including polarizability in the electrostatics was reduced from 600% to 230%. The work on the development of improved numerical methods for molecular dynamic simulations is an important component of the project. It is important to ensure that such improvements move into new versions of NAMD in a timely manner.

  Professor Kale presented recent work on the development of a suite of collective communication optimization strategies, and new parallel FFT libraries. The CS group has also demonstrated (in a separately funded project) that molecular dynamics can be scaled to the planned BlueGene/L machine with 128K processors. The close collaboration between the CS researchers and the biophysics team is very impressive, and fairly unique.

## II. Roadmap 2003-2006

- VMD Development Goals

  One of the primary goals targeted for VMD development is to improve its molecular representations, placing special emphasis in areas that enhance and facilitate production of publication quality images. For better appreciation of three-dimensional representations of proteins and complex structures, future versions of VMD will include expanded movie-making features allowing users to visualize more information

than is presently possible. Future VMD developments are also aimed at improving performance and the ease-of-use interactive molecular dynamics simulations, to develop inexpensive force-feedback input devices, and to allow users to run simulations on-demand through BioCoRE and the Grid. Plans for the introduction of plugins and programmable shading will substantially enhance the flexibility of this system and incorporate better visualization techniques into VMD technologies.

- NAMD Development Goals

  The Resource plans to develop NAMD3, a major new version of the highly scalable molecular dynamics code NAMD. NAMD3 development will focus on greatly increasing the modifiability, expandability, and maintainability of the program by devising new plug-in capabilities for individual users that will allow researchers to customize programs for their own needs. NAMD3 will also improve the usability and performance on desktop machines, clusters, and large supercomputers. This will be accomplished by exploiting the new capabilities of the Charm++ parallel programming system developed through this resource. NAMD3 design will also facilitate interoperability with the CHARMM and Amber programming systems that are currently used by many researchers. New features that will greatly facilitate use by the modeling community, such as polarizable force fields and implicit solvation of proteins, will be added.

- BioCoRE Development Goals

  The stated goal of of the BioCoRE group is to achieve adoption by the biomedical community. One significant planned enhancement to the Job Management tool will allow jobs to be chained and reduce the number of steps required to submit them. Another improvement to the Collaborative Visualization tool will make it easy for researchers to correspond in interactive sessions. Additional research programs, such as AMBER, BLAST, and GAMESS will be integrated into BioCoRE such that scientists can use BioCoRE to access tools and features that they are already used to. To achieve the goal of increasing the numbers of researchers using this interactive system, substantial effort will be made in increasing training opportunities for graduate students, postdoctoral fellows and principal investigators in future classes and Summer School programs based on the University of Illinois campus. It has been suggested that these efforts are extended and that training sessions in other places, including the faculty of biochemistry are held. Modeling courses on other campuses are proposed and that the selection for students at the Summer School should be from as brad a base as possible. The programming API will be expanded to allow scientists to fully interact with their BioCoRE data. Evaluations that are on-going are intended to expand the community of contributors,

develop second generation prototypes of the modules taught for the first time this past summer and refine the collection and interpretation of usage data.

Future plans for VMD and NAMD include a shift toward a more modular architecture that will facilitate the insertion of code developed by various collaborators. Such a shift is important. As these packages continue to develop and the user community grows, it is both increasingly hard and increasingly inefficient for all development to occur at the Resource. To the same extend that the applied projects involve a large number of senior external collaborators, the work to add new methods and new functionality to NAMD and VMD should also include external collaborators. An "open source" development model can be used where the Resource retains control of the code license and controls the code that goes into the official releases, but a few external collaborators are trusted to contribute code for key subsystems.

As NAMD becomes a more open system, and as the community of people developing NAMD code increases, there will be a need to improve support for CHARM++, in particular to provide a modern and fairly complete Application Development Environment.

There is a significant effort, mostly funded by NSF, to develop a "cyberinfrastructure" that supports collaborations between geographically distributed research teams, and aids their access to shared data and computational resources. There are significant investments in the generic "grid" cyberinfrastructure and specific investments to support defined research communities with common data formats, ontologies and tools. The BioCoRE system should be developed further in the light of this major NSF effort and possible ties with the NSF cyberinfrastructure initiative should be explored.

The Resource lost its senior administrator, who was heavily involved in user satisfaction surveys. It is important to replace this person and continue this important activity.

## III. Molecular Modelling Projects

Dr. Emad Tajkhorshid summarized recent progress on molecular modeling. These included:

- Simulation of aquaporin membrane channels. This project is one the first reports completely describing transport of materials across the membrane in full atomic detail and resulted in discovery of a novel mechanism for selectivity against proton transfer, the energetics associated with stereoselective permeation of sugar molecules through the channel, and calculation of osmotic and diffusion permeability for direct comparison with experiments.

- Interactive molecular dynamics (IMD), a method developed in the Resource for interactive manipulation of MD simulations. The first application of this method to a biological problem, namely stereoselective function of enzymes and channels, was presented.

- MD Simulation of photoisomerization of the retinal chromophore in bacteriorhodopsin by applying excited state forces calculated within the protein matrix.

The presentation by Prof. Klaus Shulten described ongoing projects in the following categories:

- Nanobiotechnology. These include nanopores for DNA sequencing, scaffold proteins for nanosize membrane models, fluidics for nanotubes.

- Major collaborations with experimental groups. As evidenced by folding of lambda repressor, forced movements within Holliday junctions, pathology of human aquaporin mutants, mechanical properties of ubiquitin, fibril formation of GB1 mutants, interaction of fibronectin with integrin.

- Mechanisms of membrane channels. Especially, gating of the potassium channel KvAP, mechanism of the chlorid channel ClC, gating of the mechanosensitive channel MscS).

- Mechanism of ATP synthase. These involve the link of stalk rotation to variation of binding sites, quantum chemistry of ATP hydrolysis/synthesis reactions during functional variation of binding sites, and explanation of key functional ATPase mutants.

- Mechanistic studies of very large systems. Such systems include the light harvesting in photosystem 1 and 2; dynamics of DNA loop formation and protein during lac repressor; CAP - DNA interaction; mechanical properties of flagellin complexes.

- Conceptual and methodological developments. These include continued development and application of interactive MD; integrating the Car-Parinello method into NAMD; and cross-ensemble simulations with NAMD.

These projects are among the most imaginative in the field of biomolecular computer simulation Backed in 2003-2004 by one of the largest awards of computer time at the NSF centers, they amply demonstrate the continued high level of activity of the Resource. The projects arose largely because the Resource attracts experimental researchers from across the US and from all over the world seeking to engage computing into their investigations and can select the best scientists for collaborations. The PI has also assembled a first

rate group of postdoctoral and graduate students who clearly enjoy working with each other and with Professor Schulten. If it were not for the fact that most projects have already far advanced during the past year of terascale computations, one could easily consider the efforts overly ambitious; but the impressive publications stemming from last year's work tell another story, that of a watershed development in biology where the terascale computer has joined beam lines and NMR instruments as an irreplaceable research instrument.

As a suggestion to the research efforts, the committee encourages the group to take advantage of its expertise and capabilities to carry out simulations of identical systems using different force fields (e.g., CHARMM, AMBER, GROMOS). They are in a unique position to test the robustness of simulations to answer questions regarding the reliability and transferability of force fields on large systems. This would be a very valuable contribution to the simulation field.

**IV. Service, Dissemination, and Training**

- Service

  The Resource serves the biomedical community, primarily by developing software, supporting it, and training users. A measure of the Resource's impact is fact that there were over 275,000 visitors to its web site in 2002. The software user community is large (over 33,000 VMD, 7000 NAMD, and 700 BioCoRE registrants) and a recent user survey found general satisfaction with the software and support. The success of the Resource has led to increasing demands for support from an increasingly diverse set of users. These increasing demands will be addressed by improved documentation and tutorials and by exploring and developing new community-based solutions. The substantial expertise of the Resource is made available via direct technical advice, by the evaluation of new technology, and by hosting long-term visitors and outside users. The Resource hosts regular on-campus seminars by experts in a variety of fields. These highly successful services will be continued.

- Dissemination

  The goal of the Resource is to maximize the impact of its research and development on biomedicine. Dissemination is an important means of achieving this goal, and the dissemination goals of the Resource are to reach as many biomedical users as possible, and increase the overall visibility of the Resource. To that end, the Resource conducted a two-week summer school in 2003. It also posts a rotating list of research highlights on its web page, has created a searchable publications and seminar databases, has made tutorials for its major applications, and has produced a VMD Image gallery. Regarding publications, the Resource produced 77 refereed articles, 128 talks, and 37 posters during 2001-2003. It also participated in various

printed media publications and press releases. Over 200 major biomedical sites link to the Resource, and images and movies produced by the Resource are often found on journal and book covers, or in conference presentations.

- Training

  The Resource has recognized the importance of training as a critical need for the education and professional growth of scientists. It has created new tutorials for NAMD and VMD, to help new and current users learn the full capabilities of the tools it provides. The 2003 Summer School provided an opportunity to teach macromolecular modeling techniques to a class of 80 participants, as well as to use their feedback to extend and improve the teaching material for future training efforts. Through its Internet site, the Resource shares its training tools, and it maintains a mailing list in order to support them. BioCoRE continues to grow as an education tool, providing a communication channel for users to ask questions, and as a repository for instructional material. The Resource intends to explore and develop innovative ways for online education, to aid the research community as a whole.

The Resource clearly takes its commitment to Service/Dissemination and training seriously and has developed a strong, effective program. The Summer School is a significant undertaking; a high visibility, high impact activity. The deep involvement of students in the Summer School is a positive experience for the students as well as a benefit to the Resource. The plans for expanding the reach of the program through web-based technologies are positive; some thought should be given to clearly defining the different roles for on-site and on-line training. Plans to conduct the Summer School regularly were mentioned, but the period was not specified. The possibility of partnering with other organizations to make the summer School part of a broader activity (with a frequency that accounts for the needs of the community and the times constraints of the Summer School instructors should be explored. Finally, we observe that the general area of the use of simulation and visualization in education (pre-college to professional) represents a significant opportunity for the Resource to expand its user base.

**Summary:**

The overall impression of the advisory board is that the resource is continuing its outstanding efforts to develop and distribute highly sophisticated modeling software and introduce these methods to a wide community. These activities are based on a foundation of stellar research. The PI is shouldering most of the burden for running and administrating the resource. The institution needs to recognize the needs of the resource and support its further flourishing.

**Year 15 Advisory Committee**

The next advisory committee (Year 15) is scheduled to meet on July 2, 2004. The board will review our performance since Aug. 1, 2003 and will offer suggestions and comments on our planned research and development efforts. We are looking forward to critical evaluation and suggestions of the board members that would help us shape our research and development activities in an optimal manner. The following colleagues have confirmed their participation in the meeting:

- Angel Garcia, LANL, Theoretical Biophysics
- Angela Gronenborn, NIH, Structural Biology of Proteins and Nucleic Acids
- Mark Lundstrom, Purdue, Electrical and Computer Engineering
- Richard Pastor, NIH/FDA, Theoretical Biophysics
- Jeffrey Skolnik, Buffalo NY, Bioinformatics

# Organization

**Organizational Structure** The Resource web site is a center point of our organization, used internally for administrative, scientific, and computing needs, and externally as a key access point for the biomedical community to review our collaborative work and developmental efforts and to take advantage of our service, training, and dissemination activities. Virtually all of the Resource's operational data (research, development, management, and system administration) are stored and distributed internally through locally developed web-based databases. Similarly, the publicly accessible external website represents our extensive effort to communicate our science to the biomedical community, through journal articles and other papers, various media (images, movies, streaming video) capturing our science, summaries of Resource research areas, access to all Resource-produced software, a list of our services, educational, and other content reflecting the work of the group.

The Resource's web site represents our way of seeing and doing things both within and beyond the Resource's formal boundaries, and also represents what we view as the mission of the Resource. Recent additions to our external website include extensive documentation of our 2003 summer school, including all lectures slides and videos of lectures*, the addition and expansion of documentation about our computational system useful to both users and system administrators.

The webs site features also a regular series of highlights that cover the main research and development evernts of the Resource. We have accumulated over the years 2001-2004 about 50 highlights that have found much praise in the community†.

K. Schulten (Professor, Physics, Beckman, Biophysics, Chemistry) is the Principal Investigator and Program Director of the Resource. E. Tajkhorshid (Assistant Director for Research), L. Kale (Professor, Computer Science) and R. Skeel (Professor, Computer Science) are Co-Principal Investigators. The Resource is located at the Beckman Institute for Advanced Science and Technology and K. Schulten, the Resource Director, administratively reports to the Institute Director. The Institute Director reports to the University of Illinois Vice Chancellor for Research. The Advisory Committee monitors Resource activity and provides highly relevant information and experienced guidance on the scientific scope and directions of the Resource.

The Resource members come from a spectrum of disciplines, each of which contributes significantly to the intricate fabric of the Resource's goals and activities. Staff and graduate students are affiliated with fields and departments such as Physics, Computer Science,

*URL:`http://www.ks.uiuc.edu/Training/SumSchool/lectures.html`

†URL:`http://www.ks.uiuc.edu/Highlights/`

Biophysics, Chemistry, Speech Communication, Mathematics, and Electrical and Computer Engineering.

All Resource members participate in the daily operation of the facility. Members attend weekly group and subgroup meetings, are responsible for specific maintenance tasks at the Resource, attend and present talks in group seminars, and keep continuously informed by spending time at the Beckman Institute as well as through email, various BioCoRE project groups, and the Resource's internal web site which lists meetings, seminars, group jobs, and more.

The PIs and affiliated faculty, in consultation with the other Resource members, determine collaborative and service projects. Selection of technological research and development projects at the Resource is determined by the following criteria:

- Relevance of research to the biological and medical sciences
- Quality and originality of research and conceptual approach
- Computational demands of the research project
- Novelty of algorithmic strategies required for the project

Continuous interactions with collaborators and ongoing critical evaluation of the projects ensure relevance, progress and adherence to the criteria outlined above. Local and remote computer time is allocated to projects as needed.

The web-based Resource manual, as well as other useful documents available on our internal site serve as guidelines for new members and as reference resources for all members.

The continually evolving internal site reflects short-and long-term objectives and describes the Resource's structure and daily procedures; it specifies policies and guidelines; it contains a job list detailing the maintenance tasks assigned to Resource members; it offers detailed information on reports, proposals, and special events. The internal site has a vital role in streamlining and systematizing the Resource operation via tips and information on the Resource's internal processes, and on Beckman and UIUC facilities and procedures.

**How to Acknowledge Resource Support** A prominent link on the front page of the Resource's external site[‡], as well as links at each application website, leads users and beneficiaries to guidelines on how to acknowledge Resource support in several ways, depending on resources used.

[‡]URL:`http://www.ks.uiuc.edu/Overview/acknowledge.html`

# Service, Training and Dissemination

## Introduction to Service, Training and Dissemination

Our service, training, and dissemination efforts are boundary-spanning activities through which we transfer the outcomes of our work and deliver technologies and knowledge to the biomedical community. These core activities can be classified into two general, sometimes overlapping, functional areas:

I. Technological development to create research tools and methods

II. Research and collaborative projects that use and benefit from the tools

Both of these activity areas have vast potential and practical implications for the Resource and the biomedical community at large. The outcomes of our technological developments and the results of our collaborative efforts are transferred to the biomedical community via our broad and numerous service, training, and dissemination activities.

Forces such as the huge genomic data revolution and the increasing pace of structure discovery, the explosive progress in hardware development and web technology, along with other factors, have infused renewed energy and urgency to our activities and are reshaping our scope and practices daily. The growth of the Resource continues, with 47 members (graduate assistants, postdoctoral associates, developers, faculty, administrative and technical staff), up from 40 last year; the number and size of systems modeled are unmatched; and, our computational resources are much larger than ever before and are effectively utilized.

Thanks to the web, the Resource's visibility has expanded greatly, and with that, the service, training and dissemination opportunities, and the complexity of our relationship with our environment have widened tremendously.

In the past year we have continued to rely on web technologies as our key service, training and dissemination vehicles. Our emphasis on web technologies allows us the flexibility to make our technological developments and collaborative efforts accessible across increasingly blurry organizational boundaries. Immense opportunities for better administration, service, training and dissemination are available now, but with them come related issues (such as intellectual property, ownership, copyright matters, licensing, etc.) that have to be considered and addressed.

Our efforts over the past year have been to work to make training as prominent on our website as our service and dissemination activities. The Resource conducted a substantial summer school effort, with the content of a year 2003 summer school being added to our website to further expand our training offerings. A year 2004 summer school will be held in June 2004; six further summer schools are planned between August 2004 and April 2005 with all content available on the Resource web site.

## Service

The Resource offers the biomedical community a variety of services as outlined below. Most of the services are well documented on our web site and, whenever possible, are completely web-based for easy access and use. The Resource is known, in particular, for its effective support of scientific collaborations, as evidenced by the collaborative projects outlined earlier in this report.

**Computational Resources**. In the past year the Resource's computational facilities have benefited members, their collaborators, and others engaged in research projects related to Resource expertise and areas of study.

119 researchers have used the Resource's computational facilities (50 local, 69 remote). As of June 2004, the Resource will have experienced an increase of 56% in shared file storage space compared to the same period a year ago (from 4.5 to 7.0 TB), with plans to reach 10 TB in the near future. In that same period, the Resource increased its local computer power by 100% and external supercomputer time has again been allocated. The Resource's local visualization capacity has grown in the past year by 12.5%.

Our knowledge of visualization solutions, large-memory computers, web utilization, and computational clusters has been of specific use to the biomedical community and to the scientific community in general; many researchers and organizations have requested and received our technical advice for the development of their local facilities. These include (in chronological order starting in June 2003):

- University of Illinois at Urbana-Champaign, Coordinated Science Laboratory (haptic devices)
- University of California at Irvine (cluster building)
- University of Technology Sydney (cluster building)
- University of California at San Francisco (cluster building)
- Northwestern University (wireless networks)
- University of Washington (cluster building)
- Asbury College (cluster building)
- Indiana University (cluster building)
- Duke University (cluster building)
- University of Michigan (cluster building)

- University of Illinois at Urbana-Champaign, Chemistry (Linux vendor recommendations)
- Beckman Computational Electronics Group (network architecture)
- University of Houston (cluster building)
- TU-Berlin (cluster building)
- University of Illinois at Urbana-Champaign, Education (data retrieval)
- Beckman Institute Systems Services (gigabyte card selection)
- Beckman Imaging Technology Group (advice on RAIDs disk plans)
- University of California at San Diego (cluster building)
- Cambridge University (consultation on SGIs and Octane2)

The Resource's technology area has kept abreast of the latest developments in the market, in particular, by maintaining relationships with leading vendors and testing our software on pre-released platforms and boards produced by Sun Microsystems. Among other benefits to our users, such cutting edge testing increases the likelihood of easily porting our software once the hardware is available on the market.

**Resource Collaborations**. Through collaborations between members and experimentalists, the Resource provides services to groups and individuals who lack the computational resources and skills themselves. Information on the content and scope of the Resource collaborative projects is available earlier in this report. The collaborations anchor the Resource in highly relevant applications and ensure that our researchers are aware of real-world challenges.

**Resource Software**. The Resource is engaged in intensive development efforts and technology transfer. We distribute a number of software packages, particularly VMD, NAMD and BioCoRE, as well as a number of smaller programs. All Resource-developed programs, binaries and source, are freely available on our web site for easy accessibility, employing where needed a unified distribution mechanism.* In this report we are focusing on the distribution and support accomplishments of VMD, NAMD and BioCoRE, in the past year.

**Use of VMD, NAMD, and BioCoRE**. The VMD, NAMD and BioCoRE packages are developed, maintained, and distributed by Resource staff. The staff also offers extensive

*URL:`http://www.ks.uiuc.edu/Development/Download/download.cgi`

user support and has turned the Resource web site into a leading and a widely recognized distribution resource for biomedical software.

The number of VMD registrants is currently 42,363 (an increase of 13,305 in the last year) of which 9,564 are repeat users. The latest version, VMD 1.8.2, boasts 8,133 users, of whom 1,636 are NIH funded. VMD has been downloaded 34,318 times in the past year.

NAMD has 9,282 registered users (an increase of 3,293 in the last year), of whom 1,809 are repeat users. 1,488 (16%) of NAMD users are NIH funded. NAMD has been downloaded 9,332 times in the past year.

BioCoRE has 851 registered users (an increase of 259 in the past year), involved in 228 projects (compared to 158 a year ago). 94 projects within BioCoRE have been reported as either fully or partially NIH-funded.

The software release schedule of the Resource's lead programs reflects great productivity and lively activity:

- VMD: 1.8.3 approaching beta; 1.8.2 was released in December 2003
- NAMD: 2.6 expected June 2004; 2.5 released September 2003
- BioCoRE: Incremental updates every few weeks;[†] beta version of next generation environment May 2004.

**Software Licensing**. The Resource maintains ongoing discussions with industry, the UIUC Technology Management Office, and others to develop special licenses for our software. During the last year, the Resource negotiated the release of many of our MDTools and the majority of our VMD plugins under the new UIUC Open Source License, allowing the software to be more freely modifiable and more freely distributable than any of our releases to date. This more permissive licensing scheme allows our users to tie in more closely to our software, and thus to customize it to their own scientific needs. Further, it encourages third-party developers to create software that interfaces to Resource applications.

**Website Popularity**. The appeal and usability of the Resource web site continues to bring in growing numbers of unique visitors. (A visitor is defined as an individual machine accessing a web page on our site; note that this is a much more conservative and accurate method of measuring web traffic than mere web hits.)

In the past year the software sections on our web site had been visited as follows:

[†]URL:`http://www.ks.uiuc.edu/Research/biocore/announce/changeLog.shtml`

| | Total | Month Avg. |
|---|---|---|
| VMD | 174,152 | 14,512 |
| NAMD | 53,693 | 4,474 |
| BioCoRE | 23,826 | 1,985 |

Table 1: Application web site visits

All three sections show a significant increase in site visits compared to the annual averages the year before (VMD +59%; NAMD +25%; BioCoRE +19%).

**Development, Distribution, and Use of VMD**

Below we report service rendered by the Resource through its molecular graphics and structure/dynamics analysis program VMD. The program enjoyed during the reported period significant improvements and a further drastic increase in user numbers.

**VMD** 2003-04 updates include:

- New "NewRibbons" ribbon representation with support for B–Spline and Catmull–Rom spline basis settings
- Improved depth cueing controls and features
- Support for high quality alpha–blended transparency
- New "draw multiple frames" feature for drawing the superposition of multiple molecular dynamics trajectory frames
- Coloring-by-timestep to aid in visualization of superimposed trajectory frames
- Significantly improved the visual quality of isosurface representations
- New RMSD alignment plugin
- New "autoionize" plugin for adding ions to solvated systems
- New file reader plugins for Amber "binpos", Autodock grid maps, BRIX electron density maps, CCP4 electron density maps, Charmm coordinate files, CPMD files, Delphi "phi" potential maps, DSN6 electron density maps, GRASP "grd" potential maps, Molden files, XtalView "fsfour" electron density maps, Gaussian "cube" files, and "XYZ" files

**VMD Posters/Presentations/Demos/Tutorials/Talks** (local and remote, by Resource members and others who informed us):

- VMD/JMV demonstrations at Siggraph 2003 (J. Stone)
- VMD demonstrations at SC2003 (Sun Microsystems, NCRR, J. Phillips)
- VMD 3-D demo logs 5/1/2003–5/1/2004:
  - 183 VMD demos in the NCSA CAVE
  - 51 VMD demos in the Resource facility

**Scope of VMD User Support:**

- 897 unique correspondents sent support requests in 2003-2004
- 7,025 emails issued to/from `vmd@ks.uiuc.edu` in 2003-2004
- Local face-to-face support has been provided

181 individuals outside of the Resource currently have access to the VMD CVS tree revision control system.

**List of papers citing VMD:** A literature search in April 2004 through ISI Web of Knowledge yielded 177 published papers that cited the VMD origin paper [104] over the past year:

1. J. F. Ying, K. E. Kover, X. Y. Gu, G. X. Han, D. B. Trivedi, M. J. Kavarana, and V. J. Hruby, "Solution structures of cyclic melanocortin agonists and antagonists by NMR." *Biopolymers*, 71:696-716, 2003.
2. E. Tajkhorshid, A. Aksimentiev, I. Balabin, M. Gao, B. Isralewitz, J. C. Phillips, F. Q. Zhu, and K. Schulten, "Large scale simulation of protein mechanics and function." in *Protein Simulations*, 66, *Advances in Protein Chemistry*, 2003, 195+.
3. B. G. Nielsen, M. O. Jensen, and H. G. Bohr, "The probability distribution of side-chain conformations in Leu and Met enkephalin determines the potency and selectivity to mu and delta opiate receptors." *Biopolymers*, 71:577-592, 2003.
4. K. Tsurusaki, S. Takeuchi, and T. Deguchi, "Crystallization of an entangled ring polymer: Coexistence of crystal and amorphous regions." *Journal of Macromolecular Science-Physics*, B42:545-557, 2003.
5. J. F. Preston, J. C. Hurlbert, J. D. Rice, A. Ragunathan, and F. J. St John, "Microbial strategies for the depolymerization of glucuronoxylan: Leads to biotechnological applications of endoxylanases." in *Applications of Enzymes to Lignocellulosics*, 855, *Acs Symposium Series*, 2003, 191-210.

6. A. J. Petrella, N. K. Roberts, D. C. Craig, C. L. Raston, and R. N. Lamb, "A heterobimetallic K2Ti2 complex incorporating two calix 5 arenes: A diverse array of metal-ligand interplay." *Chemical Communications*, 1728-1729, 2003.

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**Development, Distribution, and Use of NAMD**

Below we report service rendered by the Resource through its molecular dynamics program NAMD. The program enjoyed during the reported period significant improvements and a further drastic increase in user numbers. The program is widely considered as uniquely satisfying the demand for an effective program on the new generation of teraflop parallel computers.

**NAMD** 2003–04 enhancements include:

- Ability to read trajectory files to analyze interaction energies.
- Reduced memory use for highly bonded structures such as Si crystals.
- Tcl scripting implementation of replica exchange method.
- Port to NCSA TeraGrid (Itanium 2) and Tungsten (Xeon) clusters.

- Port to x86-64 processors (Opteron and Athlon 64) running Linux.
- Port to IBM Blue Gene/L massively parallel supercomputer.
- Port to Clustermatic 4 (Bproc 4) Linux cluster management system.
- Port to and verification of Charm parallel runtime system release 5.8.
- Enhanced performance on gigabit ethernet due to TCP network protocol.
- Enhanced performance on Pentium 4 and Xeon due to Intel compiler.
- Enhanced performance on Mac G4 and G5 due to IBM compiler.
- Requirements analysis and design of NAMD 3 continues.

**NAMD Honors and Awards:**

The Standard Performance Evaluation Corporation plans to include the full parallel version of NAMD in the next SPEC HPC benchmark suite. This suite measures the performance of high-end computing systems running industrial-style applications and is especially suited for evaluating the performance of parallel and distributed computer architectures. The serial NAMD kernel benchmark developed and submitted last year for the SPEC CPU 2004 benchmark is still under consideration.

**Posters/Presentations/Demos/Tutorials/Talks** (local and remote, by Resource members and others who informed us):

- June 2, 2003, *Scaling Molecular Dynamics to 3000 Processors with Projections: A Performance Analysis Case Study*, Terascale Performance Analysis Workshop, International Conference on Computational Science 2003, Melbourne, Australia
- June 2-13, 2003, Summer School on Theoretical and Computational Biophysics, Urbana, Illinois
- July 12, 2003, *University of Illinois Software Integration Opportunities*, Joint Amber/CHARMM Developer's Symposium, La Jolla, California
- November 19 & 20, 2002, *NAMD, VMD, and BioCoRE*, NIH NCRR booth, IEEE/ACM SC2003 Conference, Phoenix, Arizona
- March 23, 2004, *Molecular Dynamics Applications: NAMD*, Angelo Rossi (IBM) and Joachim Hein (University of Edinburgh), ScicomP 9 Conference, Bologna, Italy

**NAMD Availability in Supercomputer Centers:**

- Pittsburgh Supercomputing Center
- National Center for Supercomputing Applications
- San Diego Supercomputer Center
- Leibniz Computing Centre at Munich
- Deutsches Krebsforschungszentrum (German Cancer Research Center)

**Scope of NAMD User Support:**

- NAMD-L email list and NamdWiki editable web site created in September
- 185 subscribers and 987 postings to NAMD-L mailing list
- Searchable NAMD-L archive and NAMD User's Guide
- Over 1700 email messages to/from users in the past year
- Local face-to-face support has been provided

There are currently 117 users with access to the NAMD source code repository.

**List of papers citing NAMD:** A literature search in April 2004 through ISI Web of Knowledge yielded 55 published papers that cited the NAMD origin paper [35] over the past year:

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**Sites with Links to NAMD Site** (Google, May 2004): 130 domains; 160 sites; 174 pages.

### Development, Distribution, and Use of BioCoRE

Below we report service rendered by the Resource through its collaboratory tool BioCoRE. The program enjoyed during the reported period significant improvements and starts to become more widely adopted by the community. BioCoRE is ideally suited for making the great investment into the US computational grid eminently useful for biomedical research.

**BioCoRE** 2003-04 updates include:

- Beta version of new collaborative environment
- Improved interactions with VMD for online collaborative emphasis
- Improved interactions with user's email to aid in ubiquity
- Improvements to scalability, particularly with respect to the Control Panel interactions.

**BioCoRE Evaluation** The BioCoRE evaluation component continued its efforts in data collection and prototype creation as a means of understanding user needs and realizing those needs in the collaboratory. Data collection efforts included the BioCoRE 2003 user survey, in which registered users were asked to complete a web-based survey meant to capture user demographics, the importance of BioCoRE features to users, questions based in usability concepts, perceptions of user support, preferences for future features, overall satisfaction and impact on work, and reactions to open questions. To supplement the utility of several measures utilizing unobtrusive data collected by BioCoRE, social network measures (measures that describe social ties between persons in groups) were explored as descriptors of interaction within and between collaboratory projects. Prototype creation and refinement activities included the addition of another feature to the BioCoRE Job Management Tool, specifically a 'job chain' tool that allows users to submit a series of jobs that use the same files and settings as a previously submitted job, with the exception of what is changed in each job's input file. A File Management Prototype that provides for easily uploading, naming, deleting, moving and copying both single and multiple files was developed, including a feature meant to retrieve files from remote computer systems. A new prototype of the VMD Saved States tool, that allows BioCoRE users to share views in VMD via BioCoRE, was also assessed. To encourage review and input from the biomedical community, all prototypes were posted on the BioCoRE home page.

**BioCoRE for Training** BioCoRE proved to be an indispensible training tool during the 2003 Summer School (see p. 14). In addition to lab assistants who were available for solving problems during the hands-on sessions, students could also obtain help using the chat capabilities of BioCoRE. They were able to exchange files and other information using the BioCoRE Documents and Notebook components. The students' planning for activities outside the lab was largely coordinated through BioCoRE.

**BioCoRE Posters/Presentations/Demos/Tutorials/Talks** (local and remote, by Resource members and others who informed us):

- BioCoRE demonstrations at SC2003 (J. Phillips)
- Frederica Darema, NSF Program officer
- Bret Peterson, Project Officer NIH NCRR
- Education, Outreach and Training personnel, NCSA
- Tricia Barker, NCSA Journalist
- June 2-13 NSF Summer School (approximately 100 participants) BioCoRE demo and explanation of use for students

**Scope of BioCoRE User Support:**

- 365 emails issued to/from `biocore@ks.uiuc.edu` in 2003-2004
- 1,271 chat messages sent to the BioCoRE public help project within BioCoRE itself.

**List of papers citing BioCoRE:** A literature search in April 2004 through the ISI Web of Knowledge yielded the following citations of the BioCoRE origin paper [103]:

- M. Dittrich, S. Hayashi, and K. Schulten, "On the mechanism of ATP hydrolysis in F-1-ATPase." *Biophysical Journal*, 85:2253-2266, 2003.
- T. A. Finholt, "Collaboratories." *Annual Review of Information Science and Technology*, 36:73-107, 2002.
- R. Phillips, M. Dittrich, and K. Schulten,"Quasicontinuum representations of atomic-scale mechanics: From proteins to dislocations." *Annual Review of Materials Research*, 32:219-233, 2002.

**Sites with Links to BioCoRE Site** (Google, April 2004): 38 domains; 41 sites; 51 pages.

**Software Evaluation**

We believe in close interactions with our users and in involving them in the development process through various channels. This helps us to ensure the relevance of the programs, their high quality and also the loyalty of the users who realize that their voice is actively sought and seriously considered in development decisions. The mechanisms we use include a standard feedback form on all software front pages (connected to the software database for quick assessment purposes), explicit encouragement to users to contact developers via email, directions on how to report bugs, user meetings, user interviews, and periodic user surveys.

The latest software surveys we conducted for VMD[‡], NAMD[§], and BioCoRE[¶] were conducted through March-May of 2003. Table 2 presents ratings for meeting user needs, support meeting expectations, impact on work quality, and overall satisfaction. Copies of the evaluation reports are available at each application's website.

[‡]URL:`http://www.ks.uiuc.edu/Research/vmd/survey/report2003/vmdsurvey2003rep.pdf`

[§]URL:`http://www.ks.uiuc.edu/Research/biocore/evaluation/Misc/NAMD_2003_Survey_Report.pdf`

[¶]URL:`http://www.ks.uiuc.edu/Research/biocore/eval/surveyData/BioCoRE_2003_Survey_Report.pdf`

Survey results indicate that the majority of VMD users are affiliated with academic institutions (84%) and use VMD for research purposes (81%), with some of this research funded at least in part by NIH (20%). Nearly half of users (46%) consider themselves moderate-expert users of VMD, and just over half of VMD users are repeat users of the program (52%). While VMD is used on several different computer platforms, the most popular is Windows (40%), followed by Linux (37%). Of those respondents expressing an opinion (i.e., not answering 'unsure' on the survey), 92% report that VMD developers respond to their requests, and 75% indicate the VMD-L mailing list is useful.

A large proportion, 41.8%, of NAMD users has downloaded more than one version of the program. The majority of NAMD users are affiliated with academic institutions (81%), and most use the program for research purposes (82%). Moderate to high levels of expertise in macromolecular modeling are reported by 72% of users, with 38% reporting similar levels of expertise in using NAMD. NIH funding supports the work of 16% of users, who typically run NAMD on a local Linux cluster (60%). Of those respondents expressing an opinion (i.e., not answering 'unsure' on the survey), 93% indicate NAMD developers are responsive to their requests.

Survey results indicate that the majority of BioCoRE users are affiliated with academic institutions (96%) and use BioCoRE for research purposes (89%), with more than half indicating research funded at least in part by NIH (52%). Most BioCoRE users employ local computer resources to run large computational jobs (71%), and consider themselves proficient software users (73%). Of those respondents expressing an opinion (i.e., not answering 'unsure' on the survey), 93% indicate BioCoRE developers are responsive to their requests.

| Total N for survey* | VMD (2,146) | NAMD (452) | BioCoRE (44) |
|---|---|---|---|
| Meets needs | 67%:27%:6% | 64%:30%:6% | 55%:24%:21% |
| Support meets expectations | 48%:48%:4% | 53%:41%:6% | 67%:29%:5% |
| Positive impact on work quality | 63%:30%:6% | 59%:35%:7% | 60%:29%:12% |
| Satisfied overall | 77%:19%:3% | 77%:20%:4% | 61%:26%:14% |
| *Number of responses varies by question. | Percents are the Agree%:Unsure%:Disagree% responses to survey questions | | |

Table 2: VMD/NAMD/BioCoRE Survey User Profiles, 2003

### Development, Distribution, and Use of Other Software Tools and Services

Below we report service rendered by the Resource through its broad expertise in computational biology. The Resource furnished numerous software tools for biomolecular science and led its expertise in many other ways to the biomedical community.

**Lending out Expertise.** Additional service activities the Resource staff is engaged in are:

- MD Tools

  The Resource has developed, posted, and continually revises an MD Tools page[‖] off the main web page, that describes tools used in our development efforts in three areas, simulation tools, databases, and web, programming, and administrative tools. The collection of programs, scripts, and utilities helps researchers make various modeling and simulation tasks easier, and provides basic code and utilities that can be built up into larger toolsets. In the past year, 17 new packages have been added to MD Tools, all under the UIUC Open Source license, providing maximum flexibility to users.

- Visitor Program

  As part of our commitment to serve the community we host visitors[**] and provide guidance on using our and other computational biology software. In the past year we had nine visitors and we expect to host at least two more this summer. Visitors typically fund their visits, and the Resource provides computing resources and knowledge.

- User Support

  We seek to release code of high quality and with few bugs, and our local users are extremely helpful in this respect. By locally prototyping our code, major bugs are identified early on, assisting us in assuring the integrity and reliability of our products. Our user population keeps growing and consequently we are expected to invest more and more resources in user support. With over 52,400 users across our technology area, support is a major task, and we take it very seriously. Our support guidelines call for the programmers to respond to all support inquiries within 48 hours of receipt or the next business day. Nontrivial inquiries may take longer, though we strive to respond within three business days.

- Summer Schools

  The Resource organized an NSF-sponsored summer school on Theoretical and Computational Biophysics, held June 2-13, 2003 (see highlight Summer School on Theoretical and Computational Biophysics), and is presently developing another summer

[‖] URL:`http://www.ks.uiuc.edu/Development/MDTools/`

[**] URL:`http://www.ks.uiuc.edu/Overview/visitor.html`

school to be held at the University of Perth, Australia, June 7-19 . Videos of lectures from the 2003 summer school are posted at the Resource training web site.[††]

The Resource plans a series of six further week long schools between August 2004 and April 2005 at Midwest, East Coast, and West Coast locations. Funding has been promised. The schools are taught in a hands-on format giving participants ample opportunity to work through tutorials using real software tools. For this purpose the Resource has acquired with local funds 20 high-end laptops that are made available to participants for the duration of the workshop.

**Seminars 2003-2004.** In the past year we have organized and hosted 16 seminars. Our seminars are an established institution on the UIUC campus and benefit students and faculty from the Beckman Institute and other departments. We bring to our campus, with some financial support from the Beckman Institute and our NIH Resource grant, leading scientists from around the country and from all over the world. The seminars and their respective abstracts are all posted on our web site[‡‡] for easy information retrieval. Below is a list of the Resource seminars in the past year:

- May 28, 2003, Michael Seibert, National Renewable Energy Laboratory, Golden, CO. *Algal Hydrogen Production – Physiology, Process Development, and Hydrogenase Molecular Engineering*
- May 30, 2003, Saraswathi Vishveshwara, Molecular Biophysics Unit, Indian Institute of Science, Bangalore, India. *Dynamics and Hydration Pattern in ribonuclease – A Family Proteins*
- June 18, 2003, Jerome Henin, Universite Henri Poincare, Nancy, France. *Computing Potentials of Mean Force Using the Adaptive Biasing Force Method*
- June 20, 2003, Masasuke Yoshida, Tokyo Institute of Technology, Yokohama, Japan. *Rotary Catalysis of ATP Synthase*
- July 18, 2003, Ernst Bamberg, Max-Planck-Institut fuer Biophysik, Frankfurt am Main, Germany. *Channelopsin 1 and 2: A New Class of Ion Channels Gated by Light*
- November 3, 2003, Thorsten Ritz, Department of Physics and Astronomy, University of California-Irvine. *How Birds Detect the Geomagnetic Field*

[††]URL:`http://www.ks.uiuc.edu/Training/SumSchool/lectures.html`

[‡‡]URL:`http://www.ks.uiuc.edu/Services/Seminar/`

- November 17, 2003, Alexander MacKerell, School of Pharmacy, University of Maryland, Baltimore, MD. *CHARMM all-atom Empirical Force Field for Biomolecules: Recent Enhancements and Progress Towards Inclusion of Electronic Polarizability*

- January 26, 2004, Ulrich H.E. Hansmann, Department of Physics, Michigan Technological University, Houghton, MI. *Computer Simulations of Small Proteins*

- February 9, 2004, Nils G. Walter, Department of Chemistry, University of Michigan, Ann Arbor, MI. *Seeing is Believing: Structural Dynamics and Function of Single RNA Molecules*

- February 13, 2004, David M.J. Lilley, Medical Sciences Institute, The University of Dundee, Dundee, UK. *DNA Junctions and their Interactions with Enzymes*

- February 23, 2004, M. Amin Arnaout, Harvard Medical School, Massachusetts General Hospital, Boston, MA. *Crystal Structure of Integrins: New Insights into Integrin Activation and Signaling*

- March 15, 2004, Andrea Yool, University of Arizona, College of Medicine, Tucson, AZ. *Aquaporin Ion Channels: Function and Physiological Relevance*

- March 29, 2004, Joachim Weber, Texas Tech University Health Sciences Center, Lubbock, TX. *The Catalytic Mechanism of ATP Synthase*

- April 12, 2004, Ioan Andricioaei, Department of Chemistry, University of Michigan, Ann Arbor, MI. *Simulation and Modeling of DNA Polymerase Activity Under External Tension*

- April 19, 2004, Arieh Warshel, Department of Chemistry, University of Southern California-Los Angeles. *How do Enzymes Really Work: Using Computer Simulations to Examine and eliminate Catalytic Proposals*

- April 21, 2004, Hui Lu, Department of Bioengineering, University of Illinois at Chicago, Chicago, IL. *Structure-based Modeling of Protein Binding on the Genomic Scale*

- May 3, 2004, Julie C. Mitchell, University of Wisconsin-Madison, Madison, WI. *Computer Prediction of Protein Docking and Analysis of Binding Interfaces*

# Training

The Resource recognizes the vital importance of training towards the education and professional growth of young scientists. We have in the past 12 months expanded our web-based training capabilities to include not only tutorials, but also videos of summer school lectures and related lecture slides, and have continued to expand the recently added Training section on our web site.* The Resource continues expanding its web utilization and establishing a wide selection of web-based training materials that will reach a larger audience and enable a broader coverage of contemporary and relevant biomedical subjects.

In the last year we offered a variety of training opportunities capitalizing on a range of tools and media:

- Summer school programs
- On-line tutorials and workshops
- Traditional tutorials and workshops
- Off-site tutorials and workshops
- Classes
- Graduate student education

The Resource faculty are involved in programmatic instructional efforts on the UIUC campus, and in other programs in the areas of computational science and their applications in the biomedical fields and life sciences.

Resource personnel (Prof. Schulten, Dr. Tajkhorshid) served as mentors in the NIH-SEPA (Science Education Partnership Award) supported "Students Modeling A Research Topic" or SMART Teams† program. In the SMART Teams program high school students and their teachers construct physical models of proteins or other molecular structures being investigated by research scientists who work with the teams. As mentors to the SMART Team at Wisconsin's Kettle Moraine High School, Prof. Schulten and Dr. Tajkhorshid helped students see via a computer model how the aquaporin protein traffics in single-file water molecules through cell membranes without letting other molecules pass.

*URL:`http://www.ks.uiuc.edu/Training/SumSchool/lectures.html`

†URL:`http://www.rpc.msoe.edu/cbm/sepa/smartprojects04.htm`

**Summer School 2003.**[‡] The Resource organized an NSF-funded summer school on theoretical and computational biophysics, held June 2-13, 2003 at the Beckman Institute at the University of Illinois at Urbana-Champaign. The school explored a wide range of physical models and computational approaches useful for simulation of biological systems and the investigation of their function at an atomic level. The curriculum included case studies such as the properties of membranes, mechanisms of molecular motors, trafficking in the living cell through water and ion channels, visual receptors, and photosynthesis. Relevant physical concepts, mathematical techniques, and computational methods were introduced, including force field algorithms used in molecular modeling, molecular dynamics simulations on parallel computers, steered molecular dynamics simulations, and combined quantum-mechanical – molecular mechanical calculations. The workshop was designed for graduate students and postdoctoral researchers in computational and biophysical fields seeking to extend their research skills to include computational and theoretical expertise, as well as other researchers interested in theoretical and computational biophysics. Theory sessions[§] were followed by hands-on computer sessions, in which students were able to set up and run simulations following tutorials designed for the summer school by Resource members[¶].

Extensive computer resources were made available to students for their work. The two computer labs reserved by the Resource for the summer school provided students with access to 47 Sun Blade 1000s and 30 Dell Precision computers in the afternoon and in the evening. Resource members spent time as consultants in these labs, helping students with their tutorials, training students to use software, and providing advice to students on how to apply their new knowledge and skills to their favorite molecules. Further, students had access to two NCSA clusters dedicated to summer school use, an invaluable resource for the many students who had no experience in submitting jobs to supercomputer systems. Students were able to submit their jobs to the supercomputers without extensive queues, and were able to get their jobs completed in a time frame amenable with summer school goals. Access to the dedicated clusters for submission could be achieved via BioCoRE or through standard methods.

Summer school instructors included L. Kale (UIUC), M. Klein (U. Penn), I. Kostin (U. Missouri), T. Martinez (UIUC), T. Schlick (NYU), K. Schulten (UIUC), Z. Schulten (UIUC), R. Skeel (UIUC), and E. Tajkhorshid (UIUC). Resource staff also provided lectures on molecular dynamics methods, assembling clusters, and an overview of technical resources available to students.

[‡]URL:`http://www.ks.uiuc.edu/Training/SumSchool/`

[§]URL:`http://www.ks.uiuc.edu/Training/SumSchool/lectures.html`

[¶]URL:`http://www.ks.uiuc.edu/Training/SumSchool/labs.html`

Of the 219 individuals who applied to the school, 93 applicants were accepted to the summer school, with the Resource straining its resources to accommodate more than the originally planned for 80 students. A majority of attendees, 76 percent, were from US institutions. Overall, summer school attendees came from 66 different institutions, ranging from small colleges to large, well-known research universities. While most attendees were graduate students (71 percent), the summer school also attracted postdoctoral associates (14 percents), faculty (8 percent) and others.

At the end of the summer school, attendees were asked to complete an evaluation form; of the 83 forms handed out, 64 were returned, a response rate of 77 percent. Of those responding, a majority agreed or strongly agreed with statements indicating the summer school had broadened their understanding of concepts and principles in the field of computational and theoretical biophysics (88 percent), had improved their ability to carry out original research (81 percent), had improved significantly their computational skills (51 percent), taught them career applicable techniques (86 percent), and that the summer school material was relevant to their research (88 percent) and addressed their research needs (84 percent). Detailed evaluation results are available at the Resource web site.[‖]

**Summer School 2004**. Resource personnel (Prof. Schulten, Dr. Luthey Schulten, E. Villa, F. Araghi) are leading a summer school program on computational biology, to be held June 7-19 at the University of Western Australia's Institute of Advanced Study. During the first week of the school, students will receive an introduction to molecular dynamics in biological systems, and in the second week study computational and theoretical biophysics.

**Training on the Web**. The Resource has in the last year made available to the biomedical community a variety of training resources via the Resource web site and other Resource channels:

The Resource training page, which includes tutorials utilizing Resource tools, links to relevant classes and teaching tools useful for developing teaching contents and techniques, is regularly updated, with recent additions including links to all posted summer school materials.

A remarkable amount of content, including 33 lectures and 11 tutorials, from the Resource Summer School 2003 has been posted on an externally accessible Resource website dedicated to the school. Expanding this effort even further is the posting of video files of the lectures[**], allowing visitors to essentially experience the summer school via the video lectures, the posted lecture slides, and the hands-on tutorials.

[‖] URL:`http://www.ks.uiuc.edu/Training/SumSchool/eval.html`

[**] URL:`http://www.ks.uiuc.edu/Training/SumSchool/lectures.html`

BioCoRE has facilitated training through both private and public projects during the last year. The Resource Summer School 2003 utilized three BioCoRE projects open only to summer school participants, including 1) a work project where students could perform and store work, access BioCoRE tutorial materials, submit jobs to a dedicated computer queue, and talk to instructors, Resource staff, and other students, 2) an announcements project where instructors could relay messages to students, and 3) a social project where summer school participants could identify local eateries and entertainment options, post pictures, and expand their social networks. Further, NAMD developers opened a public project in BioCoRE in the last year for training purposes. In the NAMD public project, users can deposit example or problem datasets and correspond in real time with NAMD users and developers to develop their skills.

Further, in association with the World Universities Network (WUN), an international alliance of leading higher-education institutions, Prof. Schulten in May 2004 provided as part of the WUN lecture series on bioinformatics a lecture on physical bioinformatics broadcast via the Internet to audiences in participating institutions across the United States, the United Kingdom and Europe.

**Tutorials.** In the past year, tutorials on Resource software have been presented via conferences, the Resource Summer School 2003, and Resource application websites.

- VMD at the Scripps Research Institute during Siggraph, July 2003
- VMD Molecular Graphics, TCBG Summer School 2003
- VMD Molecular Graphics Perspective of Protein Structure and Function, TCBG Summer School 2003
- Visualization and Analysis of CPMD Data with VMD, March 2004
- NAMD Molecular Dynamics Tutorials, TCBG Summer School 2003
- NAMD Molecular Dynamics Methods, Part I, TCBG Summer School 2003
- Workshop on Charm++ and its Applications, October 2003

Internal Resource tutorials are offered on an as-needed basis, featuring sessions on the use of software development tools by scientists. Our internal web pages offer Resource members practical instructions on various useful subjects, such as writing and presentation skills, how to make movies and animations, document conversion, the use of publishing tools, and web design and implementation. Resource members also form learning groups around scientific and software interests. Scientists in the group have started an 'exchange' of visits program in which Resource members provide 3-D demos to other

scientific groups on campus, who in exchange invite Resource members to visit their laboratories. There are also internal groups dedicated to learning and exploiting the Apple Macintosh computer platform, and utilization of an electronic notebook program.

The Resource web site contains over 340 pages of introductory tutorials for self-training in the Resource programs VMD, NAMD, and related programs from other groups. The tutorials, also used in the training schools, proved extremely popular.

**Resource Library.** In the past year, 23 new books have been purchased to expand the Resource's already well-stocked library. To supplement the UIUC library's collection of on-line and print journals, the Resource subscribes to the following journals in the sciences and computing:

- Physics Today
- Science
- Sys Admin
- Journal of NIH Research
- C/C++ Users Journal
- Chronicle of Higher Education
- Dr. Dobb's Journal
- Linux Journal
- Nature
- Nature Structural Biology

**Doctoral Trainees.** Recent UIUC PhD recipients who received their training at the Resource are:

- Justin Gullingsrud
  Ph.D., Physics, Fall 2003
- Mu Gao
  Ph.D., Physics, Fall 2003
- Sanghyun Park
  Ph.D., Physics, Spring 2004

- Fangqiang Zhu
  Ph.D., Physics, Fall 2004

- Rosemary Braun
  Ph.D., Physics, Fall 2004

**Visitors.**[††] Now in its seventh year, the Resource visitor program provides young scientists the opportunity to receive on-site training with Resource members, with stays ranging from a week to several months. Visitors, who come with their own support, learn how to use Resource produced software and other software packages hosted on Resource computers, and benefit from the expertise and knowledge of Resource members. By the conclusion of their visit, visitors have acquired critical skills and new experiences that they can take back to their home laboratories.

While this effort-intensive initiative can be quite taxing on Resource members, the visitor initiative provides practical, useful knowledge to visitors, and serves as a vehicle for transferring knowledge back to the biomedical community. Visitors during the last year include:

- Xavier Cavin and Nicolas Ray, Universite Henri Poincare, Nancy, France (Spring, 2004)

- Jesus Izaguirre, Computer Science, Notre Dame (Summer, 2003)

- Jerome Henin, Physical Chemistry, Universite Henri Poincare, France (Summer, 2003)

- Michael Hoffman, Theoretical Physics, Universitaet Paderborn, Germany (Summer, 2003)

- Miriam Wodrich, Biology, WUN exchange student, University of York, UK (Summer, 2003)

- Ulrich Kleinekathoefer, Institute of Physics, Chemitz University of Technology, Germany (Summer, 2003)

- Nicolas Ray, Universite Henri Poincare, Nancy, France (November, 2003)

- Paul King, National Renewable Energy Laboratory, USDOE (November, 2003)

- Joel Gilmore, Physics, University of Queensland, Queensland, Australia (March, 2004)

[††]URL:`http://www.ks.uiuc.edu/Overview/visitor.html`

- Manuel Rueda, IRBB, Parc Cientific de Barcelona (February – March, 2004)

**Training Collaborations.** In cooperation with the World Universities Network exchange program, meant to foster international interactions between students and senior researchers in the field, the Resource hosted in the summer of 2003 Miriam Wodrich, an exchange student studying biology from the University of York, United Kingdom.

**Manuals and Tours.** Our software manuals have been available on the web for many years, and are regularly updated. Users of VMD wanting to learn how to modify software, write their own plugins, or otherwise extend VMD can now access a completely revised programmers guide, utilizing a new source-level documentation system called "Doxygen" that is updated nightly on the VMD website.[†] The NAMD manual and NAMD-L mailing list are now searchable via the application's website,[‡] a useful tool for users looking to find needed information without extensive browsing of documents. The BioCoRE tour,[§] that combines a tutorial with slides indicating software features and depicting its utilization, has been updated to display new features. The tour is regularly updated and developed.

[†]URL:`http://www.ks.uiuc.edu/Research/vmd/doxygen/`

[‡]URL:`http://www.ks.uiuc.edu/Research/namd/`

[§]URL:`http://www.ks.uiuc.edu/Research/biocore/tour/`

## Dissemination

The Resource's intense dissemination and outreach efforts continued through the last funding period, taking advantage of a wealth of delivery mechanisms from web-based distribution of Resource-produced papers and know-how, through talks in meetings and conferences all over the world, software distribution, news stories and press releases, demonstrations, to the use of Resource-made images in a variety of third-party publications and presentations.

The Resource published brochures and videos, and was also featured for its accomplishments in trade magazines and other printed and online media; for example, our movie of the passage of water molecules through aquaporin water channels is featured at the Nobel e-Museum website as a demonstration animation for the Nobel Prize in Chemistry for 2003.*

Stories on the Resource appeared in popular media, Supercomputer Center magazines and reports and more. All these news-making stories are posted on the Resource web site in the "In the News" section:†

- March 14, 2004 - UI-based TeraGrid largest computer net for research in world. *The News-Gazette.*
  http://www.news-gazette.com/story.cfm?Number=15622
- March/April, 2004 - Two Steps Forward. Research provides leads for possible cancer breakthroughs. *Illinois Alumni*, 16(5), 7.
  http://www.uiaa.org/urbana/illinoisalumni/
- December 22, 2003 - Metastasis - Unraveling a protein, researchers uncover mechanics of anticancer agent. *NewsRx.com*
  http://www.newsrx.com/
- December 2, 2003 - Unraveling a protein, researchers uncover mechanics of natural anti-cancer agent. *University of Illinois at Urbana-Champaign News Bureau.*
  http://www.news.uiuc.edu/scitips/03/1202schulten.html
- November 17, 2003 - InfiniCon Systems Demonstrates 10Gbps InfiniBand Cluster Running Award-Winning NAMD High Performance Computing Application at SC2003. *Business Wire.*
  http://home.businesswire.com/portal/site/home/index.jsp?front_door=true

*URL:`http://www.nobel.se/chemistry/laureates/2003/animations.html`

†URL:`http://www.ks.uiuc.edu/Publications/stories.cgi`

- September 9, 2003 - BioCoRE@ NCSA. *NCSA Access*. http://access.ncsa.uiuc.edu/Stories/BioCoRE/

**Publications** In the past year Resource members have published and/or submitted or presented a total of:

- 43 refereed articles
- 38 talks by PIs, and 10 talks or meetings attened by other group members
- 11 posters

**Talks**

The Resource PIs gave the following talks in the last 12 months:

Klaus Schulten

- April 26-30, 2003, Berlin, Germany, DFG Research Center, *Computational Modeling of the Mechanics of Living Cells*
- May 21-23, 2003, Pittsburgh, PA, From Structure to Function: Frontiers of Biological Ion Channels Workshop, *Computational Study of Substrate Selectivity in Membrane Channels*
- June 22-27, 2003, Bristol, RI, Gordon Research Conference on Photosynthesis, *PS1 Light Harvesting Dynamics*
- July 14-17, 2003, Lake Tahoe, CA, XIXth Conference on the Dynamics of Molecular Collisions, *Elementary Processes in Vision*
- July 23-26, 2003, Bonn, Germany, XI International Congress of Quantum Chemistry, *Large Scale Simulation of Protein Mechanics and Function*
- August 3-10, 2003, Villard de Lans, France, Jam Session on Biophysics, *Large Scale Simulation of Protein Mechanics and Function*
- August 10-23, 2003, Lugano, Switzerland, Summer School of Multiscale Modelling and Simulation
  - *Photosynthetic Unit from Light Absorption to ATP Synthesis*
  - *The ATP Synthesis Machine*
  - *Mechanics of Living Cells*

– *Conceptual and Methodological Challenges in Theoretical Biophysics*

- August 25, 2003, Urbana, IL Biophysics Faculty presentation, *Study of a Membrane Channel by Crystalllography and Modeling*
- September 11, 2003, New York, NY, 226th ACS National Meeting, *Molecular Dynamics Simulation of Bacteriorhodopsin's Photoisomerization Using ab initio Forces for the Excited Chromophore*
- September 29, 2003, New York, NY, Columbia University, Biological Sciences Seminar Series, *Mechanical Functions of Proteins*
- October 2, 2003, Ann Arbor, MI, University of Michigan Department of Chemistry Seminar, *Mechanical Functions of Proteins*
- October 13-15, 2003, Basel, Switzerland, Nanoforum CH-US, *Towards Understanding Membrane Channels*
- October 26-29, Ascona, Switzerland, International Workshop on Elucidating Biomolecular Networks by Single Molecular Technologies, *Theoretical Biophysics of Membrane Channels*
- October 30-31, 2003, Frankfurt, Germany, International Symposium on the Molecular Mechanisms of Membrane Proteins, *Biophysics of Membrane Processes*
- November 6, 2003, Urbana, IL, UIUC Chemical Biology Seminar, *Mechanical Functions of Proteins*
- December 4, 2003, Pasadena, CA California Institute of Technology Biophysics Seminar, *Towards Understanding Membrane Channels*
- December 11, 2003, Philadelphia, PA, University of Pennsylvania Department of Chemistry Seminar, *Mechanical Functions of Proteins*
- February 14, 2004, Urbana, Illinois, 2004 Physics Faculty Recruitment Talks, *Biophysics Theory*
- March 3, 2004, Bonn, Germany, Gustav-Stresemann-Institut, NIC Winter School 2004, *Protein Mechanics*
- March 19, 2004, Lake Tahoe, CA, International Workshop Structural Analysis of Supramolecular Assemblies by Hybrid Methods, *Multiscale Simulations of Supramolecular Dynamics Demonstrated for Lac Repressor and ATPase*
- May 18, 2004, Tempe, AZ, NSF "Workshop on the Role of Theory in Biological Physics and Materials," *Plenary Lecture*

- May 19, 2004, Santa Fe, NM, 24th Annual Conference of the Center for Nonlinear Studies, *Mechanical Functions of Proteins*

Laxmikant Kale

- May 2004, Urbana, IL, Siebel Center, UIUC *Interactive Molecular Dynamics in Parallel Supercomputers*
- April 2004, Santa Fe, NM, CAC Workshop at IPDPS '04
  - *Opportunities and Challenges of Modern Communication Architectures: Case Study with QsNet*
  - *BigSim: A Parallel Simulator for Performance Prediction of Extremely Large Parallel Machines*
  - *Performance Modeling and Programming Environments for Petaflops Computers and the Blue Gene Machine*
- June 2003, Melbourne, Australia, Terascale Performance Analysis Workshop, International Conference on Computational Science(ICCS), *Scaling Molecular Dynamics to 3000 Processors with Projections: A Performance Analysis Case Study*

Robert Skeel

- June 2003. Scientific Computing and Differential Equations 03, Trondheim, Norway

Emad Tajkhorshid

- June 2003, Holderness, NH, Gordon Research Conference on Mechanisms of Membrane Transport, *Computational Studies of Aquaporin Function and Mechanism*
- July, 2003, Long Island, NY, Computing for Biology, IBM-BNL Blue-Gene Science Workshop 2003, *Large Scale Molecular Dynamics Simulations of Membrane Proteins*
- October, 2003, Lexington, KY, Software Solutions to Large Scale Problems in Computational Chemistry Computational Chemistry GRID Conference, *Molecular mechanisms of photoactivation and spectral tuning in retinal proteins*
- November, 2003, St. Louis, MI, Multi-scale simulation of biological systems, International Conference on Systems Biology 2003, *Largest-Scale Full-Atomic Simulations of Biomolecular Processes*

- February, 2004, Baltimore, MD, 48th Annual Meeting of the Biophysical Society
  - *Electrostatics Regulation of Substrate Permeation and Selectivity of Aquaporins*
  - *Structural Basis of Substrate Permeation and Selectivity in Membrane Channels: Lessons from Non-Equilibrium Simulations*

Other Resource members gave the following talks, poster presentations or attended meetings in the past year:

- July 2003. CHARMM Meeting, San Diego, CA. (James Phillips)
- July 2003. SIGGRAPH 2003, San Diego, CA. (John Stone)
- August 2003. Multiscale Modeling and Simulation Summer School, Lugano, Switzerland. (Elizabeth Villa)
- October 2003. LACSI Conference, Los Alamos National Laboratory, NM. (Sameer Kumar)
- November 2003. SC2003 Conference, Phoenix, AZ. (James Phillips, Robert Brunner)
- February 2004. Biophysical Society $48^{th}$ Annual Meeting, Baltimore, MD. (Fangqiang Zhu, Jordi Cohen, Marcos Sotomayor, Barry Isralewitz, Marcus Dittrich, Timothy Isgro, Aleksei Aksimentiev, Elizabeth Villa, Rosemary Braun, Fatemeh Khalili-Araghi)
  - Poster: *QM/MM study of ATP hydrolysis in $F_1$-ATPase* (Markus Dittrich)
  - Poster: *Insights into the Molecular Mechanism of Rotation in the Fo sector of ATP Synthase.* (Aleksij Aksimentiev)
  - Poster: *Molecular Dynamics Simulations of a Nanopore Device for DNA Sequencing.* (Aleksij Aksimentiev)
  - Poster: *Conformation change during simulated rotation of $F_1$-ATPase central stalk.* (Barry Isralewitz)
  - Poster: *Molecular Dynamics Studies of SDS Aggregation about Glycophorin-A Transmembrane Helix Dimer.* (Rosemary Braun)
  - Poster: *Lipid Bilayer Pressure Profiles and Mechanosensitive Channel Gating.* (Justin Gullingsrud)
  - Poster: *Molecular Dynamics of Gating in the Mechanosensitive Channel of Small Conductance MscS.* (Marcos Sotomayor)

  - Poster: *Mechanical Properties of Ubiquitin Chains.* (Fatemeh Khalili-Araghi)
  - Poster: *Theory of water permeation in single-file water channels.* (Fangqiang Zhu)
  - Poster: *Lac repressor-DNA loop dynamics.* (Elizabeth Villa)
  - Poster: *Molecular dynamics simulations of isolated $\beta$–subunits of $F_1$-ATPase.* (Ulrich Kleinekathofer)

- March 2004. Annual American Physics Society meeting, Montreal, Canada (Deyu Lu)
- April 2004. IPDPS Conference, Santa Fe, NM. (Sameer Kumar, Gengbin Zheng)
- May 2004. Statistical Physics of Macromolecules, Santa Fe, NM. (Jin Yu)
- May 2004. Interactive Molecular Dynamics in Parallel Supercomputers. Siebel Center, UIUC, Urbana, IL. (Jordi Cohen, Jay Desouza, Gengbin Zheng)

**Outreach** Our outreach efforts are broader now than ever before, resulting from our increasing visibility on the web, in the software user community, in meetings, journals, and other media. Telling indicators demonstrating the impact of our outreach activities include:

- Major sites with links to our site
- Major sites that use our images [‡]
- Others publish our images
- On-site demonstrations
- Internet broadcast lectures

A recent Google search (April, 2004) yielded the following statistics regarding links to the main Resource web page: 64 pages link to us, from 56 sites in 47 domains.

There have been a total of 447,430 unique visitors to the Resource web site, an average of 46,533 per month, over the last year; also 99,328 MB was downloaded from the site. The sections most visited are shown in Table 3.

Sample education (out of 227 total), scientific resources (21 total), and computing (25 total) sites with links to the Resource web site include:[§]

*Education*:

[‡]URL:`http://www.nobel.se/chemistry/laureates/2003/animations.html`

[§]`Categorized results of a May 2004 Google search.`

| | Total Visitors | Visitors per Month |
|---|---|---|
| VMD | 174,152 | 14,512 |
| NAMD | 53,593 | 4,474 |
| BioCoRE | 23,826 | 1,985 |
| Other Research | 81,972 | 6,831 |
| Papers | 27,500 | 2,291 |
| Galleries | 17,104 | 1,425 |
| Seminars | 3,282 | 273 |
| Biosoft DB | 4,265 | 355 |

Table 3: Numbers from Apr 2003 – Mar 2004

- *University of California at San Diego: Physics Department, Chemistry Department, Keck Lab for Integrated Biology, and McCammon Biophysics Group*
  physics.ucsd.edu, chem-faculty.ucsd.edu, keck2.ucsd.edu, mccammon.ucsd.edu
- *Purdue University: Computer Science Department, Chemistry Department, Nanotechnology Simulation Hub, and Instructional Computing Services*
  www.cs.purdue.edu, www.chem.purdue.edu, www.nanohub.purdue.edu, expert.ics.purdue.edu
- *Scripps Research Institute: Amber Molecular Dynamics and Metalloprotein Database*
  amber.scripps.edu, metallo.scripps.edu
- *Cornell University: Biology Department, Molecular Biology and Genetics Department, and Medical Library*
  bio.cornell.edu, www.mbg.cornell.edu, library.med.cornell.edu
- *Duke University: Biology Department, Electrical Engineering Department, and Single Molecule Force Spectroscopy Lab*
  www.biology.duke.edu, www.ee.duke.edu, smfs.pratt.duke.edu
- *New York University: Math Department, Computer Science Department, and Computational Biology/Chemistry/Biomathematics Department*
  www.math.nyu.edu, cs.nyu.edu, monod.biomath.nyu.edu
- *Harvard University: Instructional Computing Group and Wagner NMR Structural Research Group*
  www.courses.fas.harvard.edu, gwagner.med.harvard.edu

- *University of California at Berkeley: Electron Microscopy Group and Computer Science Department*
  cryoem.berkeley.edu, www.cs.berkeley.edu
- *Yale University: Center for Structural Biology and Yale-New Haven Medical Center*
  www.csb.yale.edu, info.med.yale.edu
- *University of Pennsylvania: Center for Molecular Modeling and Biology Department*
  www.cmm.upenn.edu, www.bio.upenn.edu

*Scientific Resources*:

- *Protein Data Bank*
  www.rcsb.org
- *Biophysical Journal*
  www.biophysj.org
- *Science Magazine*
  www.sciencemag.org
- *Center for Molecular Modeling at National Institutes of Health*
  cmm.info.nih.gov
- *The Foresight Institute Nanotechnology*
  www.foresight.org
- *PhysicsWeb, Physics News and Resources*
  physicsweb.org
- *Chemistry at Harvard Molecular Mechanics*
  www.charmm.org
- *Gromacs Molecular Dynamics*
  www.gromacs.org
- *Bioinformatics Open-Access*
  bioinformatics.org
- *Ernest Orlando Lawrence Berkeley National Laboratory*
  www-vis.lbl.gov/

*Programming/Computing Related*:

- *Apple Computers*
  www.apple.com
- *OpenGL Programming*
  www.opengl.org
- *Silicon Graphics*
  www.sgi.com
- *Linux Online*
  www.linux.org
- *Java 3D Community*
  www.j3d.org
- *GNU Operating System*
  www.gnu.org
- *PovRay Objects Collection*
  objects.povworld.org
- *VersionTracker Software Downloads*
  www.versiontracker.com
- *FreshMeat Software Downloads*
  www.freshmeat.net
- *MacOSX Software Applications*
  www.macosxapps.com

The Resource responds to nearly weekly requests for permissions to use Resource images on other sites, in textbooks, papers, and talks given or written by others. We have formulated a standard response to such requests and while protecting our copyrights and ownership we have adopted an open and liberal approach in granting permission.

**Brochures** A number of brochure projects have been pursued by the Resource as a means of communicating information about our programs, research, and software. Each brochure is described below:

- *Summer School 2003*[¶] – describes the summer school pictorially and via descriptions of the program, instructors, students, evaluations, and other content.

[¶]URL:`http://www.ks.uiuc.edu/Publications/Brochures/SS03/SS03.pdf`

- *Research Highlights*[‖] – every month, the Resource posts a research highlight on the main web site that demonstrates our research interests. The Research Highlights brochure compiles the text and images used in these highlights from January 2001 through March 2004.

- *Bringing Physics to Life*[**] – portrays the philosophy and work culture at the Resource that facilitates scientific collaboration and pursuits.

Additionally, two other brochures are in development, a brochure that provides descriptions of recent attributes of the three major software applications of the group, VMD, NAMD, and BioCoRE, and a companion brochure entitled *Bringing Physics to Life* that portrays the software and computational achievements of the Resource and the persons and culture behind those achievements.

**Videos**

The Resource has expanded its video offerings via posting as streaming files videos from the 2003 Summer School[††]. Visitors to the group web site can view the lectures from each of the summer school while viewing the associated slides. In this fashion, those who were not able to attend can repeat the experience of those able to attend the lectures.

**Licensing and Distribution**

Over the last year, the Resource was able to place many components of its software packages, such as the MDTools collection of programs, scripts, and utilities, and nearly all of the VMD plugins, under the new UIUC Open Source License, a scheme that allows the software to both be modified more freely by users, and to be more broadly distributable by the biomedical community. An example is CatDCD, a tool that concatenates multiple DCD files into a single DCD file, and that can also write selected atoms into a final DCD file. The CatDCD program incorporates the DCD plugin from VMD, a step hindered by prior licensure. Similarly, users can develop other software programs that tie into VMD, IMD, and other Resource software. Such customization allows our user community to tailor the already powerful Resource software applications to their research needs. And, by making these packages available with an open source license, third-party developers are encouraged to make software that interfaces to Resource software. One example of successful software interfacing resulting from licensing changes is the ProtoMol molecular dynamics framework, which supports interactive molecular dyanmics simulations via con-

[‖]URL:`http://www.ks.uiuc.edu/Highlights/`

[**]URL:`http://www.ks.uiuc.edu/Publications/Brochures/BPTL/`

[††]URL: `http://www.ks.uiuc.edu/Training/SumSchool/lectures.html`

nections to VMD, using source code provided with the open source license.[‡‡] The open license further encourages VMD users to donate plugins, as the license doesn't restrict use of the plugin solely to VMD.

Finally, our commitment to improving our dissemination efforts have lead in the past year to significant performance improvements to our web server, a major dissemination tool of the Resource. The upgraded web server is more stable and delivers our content to the biomedical community at four times the speed of our prior configuration. Further, all group databases, including our publications database were upgraded to use the MySQL, a widely accepted database program that provides better performance and more capabilities including greater speed and longer search queries, both essential features for those searching through publications. The use of images on the Resource home page has also been reduced, to provide faster loading speeds for visitors.

[‡‡]URL: `http://www.nd.edu/ lcls/Protomol.html`

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