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   A. NAME: Klaus J. Schulten
   B. TITLE: Professor
   C. SIGNATURE:
6. DATE SIGNED (Month, Day, Year):
7. TELEPHONE NUMBER (Include Area Code): (217) 244-2212
8. FACSIMILE NUMBER (Include Area Code): (217) 244-6078
9. ELECTRONIC MAIL ADDRESS: `kschulte@ks.uiuc.edu`
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Contents

Introduction

This report describes the development, research and service activities during the 2002–2003 funding year at the NIH Resource for Macromolecular Modeling and Bioinformatics. This is the first year of a five-year funding cycle of the Resource.

The Resource for Macromolecular Modeling and Bioinformatics uses its strong research expertise do develop computational tools and methodologies for the study of cellular processes from the biomolecular to the cellular level. Tools and methodologies are made freely available to biomedical researchers and their use is facilitated by strong collaborations with biomedical scientists. With rapid growth of genomic and structural information in cellular biology, there is a great need for tools that integrate this information into physical models of the cell and the whole organism. This demands simulations of larger molecular assemblies and longer timescales than ever attempted before. It also demands, at the cell and organism level, the integration of a wider range of concepts and methods than has ever been used before, including stochastic mathematics, statistical physics, multiscale approaches, network kinetics, and whole cell modeling. The computational and methodological challenges that arise are met not only with the availability of increasingly more powerful computers, but also through our researchers ingenuity. The progress achieved over the past year, as well as pioneering applications to timely and relevant biomedical problems, is outlined below, together with broad statistics of our Resources service, training, and dissemination activities.

Summary of Research Progress

Research Software Development

Simulation as well as visualization of macromolecular assemblies demand dedicated software tools capable of handling systems that reach sizes of hundreds of thousand atoms. The Resource's modeling program NAMD and its visualization program VMD meet this challenge and provide biomedical researchers with unparalleled opportunities as outlined below. The communication needs between researchers in different institutions and between researchers and the supercomputing resources in national centers necessitate the development of an easy to use and widely applicable collaboratory environment. The Resource's web-based collaboratory software BioCoRE is designed to meet this demand.

The Resource's modeling program NAMD was recognized at the SC2002 High Performance Networking and Computing conference with the prestigious Gordon Bell Award for

The preparation of this report was coordinated by Melih Sener

unprecedented performance of a widely used software tool. Also in the past year, NAMD finally passed the Teraflop performance benchmark using 3000 processors of a computer available at the Pittsburgh Supercomputing Center. In another milestone achievement, NAMD has recently been used by researchers from the Los Alamos National Laboratory for the 5 ns simulation of the two million atom ribosome system, breaking a world record in simulated system size for a molecular dynamics simulation.

The Resource's visualization program VMD further increased its huge user base while it enjoyed the addition of key features and increased its availability across platforms. In the past year the VMD user interface has been completely rewritten, furnishing better menues, significantly improving ease-of-use. The Mac version of VMD now uses the native Mac windowing system and hardware accelerated graphics, yielding a thirty-fold improvement in rendering speed. New trajectory smoothing, coloring, rendering, and movie making features make it easy to create high quality movies for conference presentations and the web.

In the past year, efforts further developing BioCoRE have focused on feature enhancement, training capabilities, and dissemination, including a BioCoRE server now in operation at NCSA. The addition of public projects, a lab book module, and more transparent filesystem access via WebDAV is making BioCoRE an ever more substantial tool for biomedical research, research management, and training, preparing BioCoRE for widespread adoption.

Science Projects

Collaborations with experimental investigators form the basis of the research done by the Resource. This not only insures the timeliness and relevance of the projects that are undertaken, but also that the software and methods developed by the Resource remain well adapted to the needs of biomedical researchers.

Steered molecular dynamics, a method pioneered by the Resource and now widely used, is essential in meeting the challenges of multiple time and length scales imposed by the macromolecular systems studied. One such system studied by the Resource is F_1 F_o ATP synthase, the energy conversion device ubiquitous in all cells. As a consequence of our modeling efforts single molecule experiments are planned by our collaborators to test our predictions of the rotation of the F_o motor. Another application of steered molecular dynamics involves the forced detachment of the CD2 and CD58 proteins, which are surface receptors between T-cells and antigen presenting cells. A 100,000 atom simulation revealed in atomic level detail how the human immune system is strengthened through elastic adhesion. Other applications of steered molecular dynamics in the past year studied are the selectivity mechanism of the membrane channels known as aquaporins; the

mechanobiology of titin/fibronectin modules in muscle and the extracellular matrix; the gating mechanisms of the mechanosensitive membrane channels MscL and MscS; the mechanism of a genetic switch; and helix association in lipid environments.

As the next logical step in steering a molecular simulation to bridge time scales, researchers directly interact with their simulations by means of mechanical input and feedback devices. This novel method, named *interactive molecular dynamics*, was developed by the Resource over the past decade and has now been applied for the first time, namely to study the selectivity mechanism of the membrane channel GlpF. A second study utilized interactive molecular dynamics to investigate the permeation and gating mechanism of the chloride channel ClC. Methodological advances for reliable and effective computation of free energy profiles from steered and interactive molecular dynamics simulations have been realized as well.

The most important advance of interactive molecular dynamics is, that it promises to make molecular simulations as easy as molecular graphics, leading to a more wide-spread use of this research methodology, in particular, among experimentalists.

Interaction of light with living matter, such as in vision or light-induced processes in the skin, poses different challenges to biomedical researchers due to the inherent quantum mechanical nature of the processes involved. One such challenge directly relevant for vision, is the photoisomerization of retinal. A combined quantum mechanical/molecular mechanical approach has been used to investigate the mechanisms by which light energy is absorbed and stored in retinal proteins.

Other projects the Resource has undertaken in the past year include collaborative studies on the effects of pressure on protein folding and stability; on structural changes in the 4-way DNA junctions, known as Holliday junctions; on carbon nanotubes as models of biological channels; and on membrane scaffold proteins that furnish nanoscale mimics of biological membranes for pharmacological investigations.

Service, Training, Dissemination

In the past year the Resource has continued to take advantage of web technology as its key service, training and dissemination tool. Through the successful use of the web the Resource is, again, reaching the widest possible audience. Access to extensive web sources of the Resource allows users to see us, read about us, and learn to use the variety of tools, expertise and knowledge produced at the Resource.

While in the previous funding cycle our focus was mostly on web-based dissemination and services, in the last 12 months we have begun to substantially expand and develop our web-based training offerings. The growing functionality and popularity of BioCoRE

and of high bandwidth communication networks have made this goal timely and relevant. A notable example of our growing training efforts is the upcoming 2003 summerschool, *Computational Approaches for Simulation of Biological Systems*, organized by the Resource and co-funded by NSF.* Over 30,000 users now benefit from our software packages and quality support (see service on p. 85), and each month 32,000 visitors come to our web site to read our papers, view our images, and draw on the other online resources we provide (see dissemination on p. 117).

*see details at `http://www.ks.uiuc.edu/Training/SumSchool03/` and later in the training section

Highlights

Molecular Mechanisms of Energy Conversion in Cells: ATP Synthase

Most processes in living cells are powered by the molecule adenosine tri-phosphate (ATP). The energy provided by sunlight or stored in food is first converted into ATP in order to be useful for cells. The enzyme that is responsible for synthesis of ATP in cells is ATP synthase*, a complex of two molecular motors mechanically connected by a common central stalk, as shown in Figure 1. The energy generated by photosynthesis or food metabolism, which is in the form of a surplus of protons on one side of the cell membrane, is used by the membrane-bound F_o unit to induce mechanical rotation of the central stalk. This rotation is transmitted through the $\gamma\delta\epsilon$ stalk to the F_1 unit where it causes cyclic shape changes of the α and β subunits in F_1, leading to synthesis of ATP from its component parts (ADP and P_i) inside the binding pockets [1]. ATP synthase can also operate in reverse, using the energy released during ATP hydrolysis to pump protons across the membrane and generate the proton gradient. Malfunction in the energy conversion processes carried out by ATP synthase is suggested to play a role in several neurodegenerative diseases [2–6].

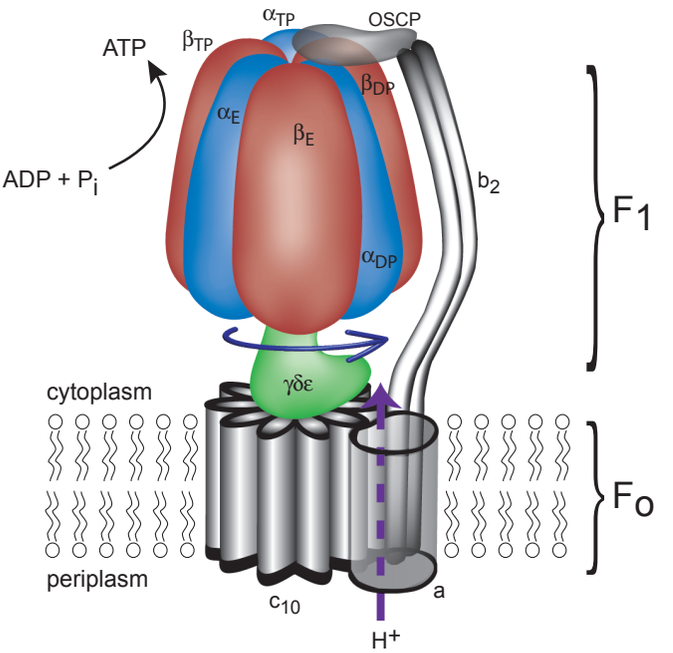

Figure 1: Schematic view of F_1F_o ATP synthase. During synthesis, the central stalk ($\gamma\delta\epsilon$) and the F_o ring (c_{10}) rotate relative to the rest of the system (direction indicated by the curved arrow). The rotation is driven by a flow of protons (H^+) across the membrane, as indicated by the vertical arrow, and causes synthesis of ATP in the catalytic sites located at the interface between neighboring α and β subunits.

The multiple time and length scales relevant to F_1F_o-ATP synthase function pose great

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

challenges to computational modeling of this system. In a living cell, a typical rate of the $\gamma\delta\epsilon$ stalk rotation is about one revolution per 10 milliseconds. This rotation is driven by the protons traveling from one side of the membrane to the other through the membrane-bound F_o unit. Inside F_o, the protons hop from one amino acid to another, the proton hopping itself being a process billion times faster than the rotation of the central stalk. To bridge this temporal gap, the Resource has embraced a new methodology of multi-scale simulations [7], linking a mathematical model capable of describing processes on a millisecond time scale to nanosecond molecular dynamics simulations performed with NAMD. The first application of this methodology to the F_o unit revealed a novel mechanism of F_o operation, extending the model suggested by our collaborator R.H. Fillingame [8]. The F_o unit is proposed to operate as a molecular roller bearing, in which the rotation of the F_o ring (c_{10}) is interlocked with individual rotation of its transmembrane helices.

Inside the F_1 subunit, mechanical rotation emanating from the base of the central stalk causes elastic deformation of the α and β subunits and, thereby, induces structural changes in the binding pockets 100 Å away. These events occur on a millisecond time scale and contrast with the actual formation of ATP in the catalytic sites, which takes place almost instantaneously once the correct protein conformation is established. To investigate this in more detail, the Resource has employed steered molecular dynamics simulations to study the elastic properties of force propagation and changes in conformation of the binding pockets upon rotation of the central stalk [9]. The simulation contained 327,000 atoms and was performed with the molecular dynamics program NAMD [10]. We were able to observe the movement of several amino-acid side chains in the catalytic sites that were consistent with synthesis events. In order to tie these results together with local properties of ATP hydrolysis inside the catalytic sites, the Resource has performed combined quantum mechanical/molecular mechanical simulations [11]. The simulations identified a novel mechanism employed by the protein for efficient ATP hydrolysis and also allowed us to characterize regions of the binding pockets likely involved in transmitting and amplifying the chemical event to cause rotation of the central stalk.

In future work, the Resource plans to advance the studies of the components of ATP synthase, and to connect the results to form a comprehensive picture of the function of the complex, capturing both its microscopic details and its behavior on physiological time scales.

Selectivity Mechanisms of Membrane Channels

All living cells use lipid molecules as the major building blocks of their cell membranes. Since both the environment and the interior compartment of a cell are mainly composed of water, lipid membranes provide barriers against undesired loss of water soluble materials from the cell, as well as intrusion of harmful compounds into the cell. At the same time, however, a cell needs to exchange desired materials with its environment, in order to maintain its metabolism and function. For this purpose, specialized proteins forming membrane channels have been evolved. These proteins form hydrophilic channels that can be used by water soluble substances, such as ions and water, to cross the cell membrane. In order to provide selective transport, membrane channels need to recognize their substrates through specific interactions. Recent developments in crystallography of membrane proteins have resulted in three-dimensional structures of a number of membrane channels. These structures have set the stage for investigating membrane channels by computer simulations in an attempt to understand at an atomic level selectivity mechanisms employed by them.

Aquaporins* (AQPs) are a family of membrane channels that provide a fast and efficient means of transport of water and other small, neutral molecules across the cell membrane [12–14]. They are widely distributed in all domains of life, including bacteria, plants, insects, and vertebrates [12–14], and play critical roles in water homeostasis of the cell. In the human body, more than ten different AQPs have been characterized, which are distributed in various organs, such as red blood cells, salivary glands, lungs, the eyes, and the central nervous system. Despite the short history of AQP research, several diseases, such as congenital cataracts, Sjorgen's syndrome, and nephrogenic *diabetes insipidus*, have already been found to be connected to the impaired function of these channels [12, 14]. AQPs in human kidneys circulate a bathtub of water a day between urinary tract and blood vessels, and therefore their malfunction result in several common afflictions.

Using large-scale molecular dynamics simulations of membrane-embedded models of AQPs, the Resource has been studying physical mechanisms underlying substrate permeation and selectivity in AQPs [15–20]. These channels function in a very selective manner: water pores of AQPs are permeable only to neutral molecules, and charged species, such as ions, are completely excluded from transport, a critical property for conservation of membrane potential. Even protons, which can be readily transported through hydrogen-bonded networks of water, as present in AQPs, are mysteriously excluded. A proton leak would dissipate a transmembrane proton gradient, which fuels the cell's metabolism. The permeation of molecules through AQPs was simulated by steered [21, 22] and interactive

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

molecular dynamics [20, 23], techniques pioneered by the Resource. These methodologies allowed us to simulate events that occur on time scales not reachable by conventional molecular dynamics simulations. Based on the results, novel mechanisms were proposed that successfully reveal the structural basis of selectivity against ions and protons in the whole family of AQPs [17, 18, 24]. The results also explain different permeation rates observed for various stereoisomers in aquaglyceroporins [20].

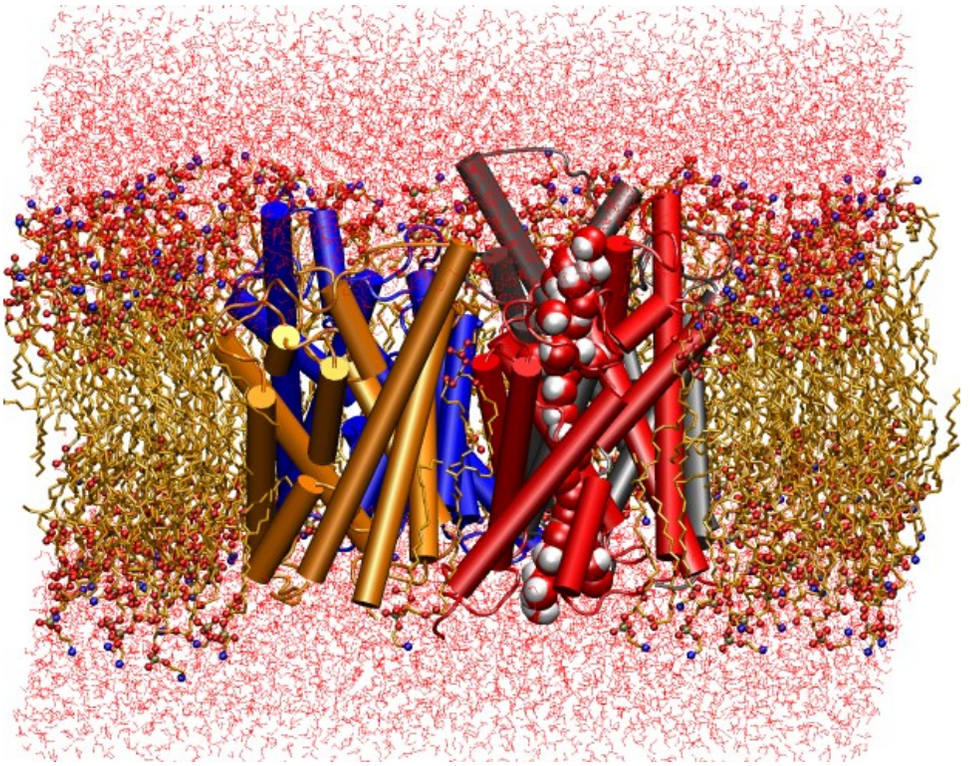

Figure 2: Simulated model of an aquaporin tetramer embedded in lipid bilayer. The diameter of the channel pore in AQPs allows water to pass only in single file. Size restriction is a critical requirement for selectivity of channels in general. In AQPs, single file substrate transport proved necessary for their selectivity against protons [18] and for stereoselective transport of sugar molecules [17, 20].

AQPs employ a combination of size constriction, specifically positioned hydrogen bonding sites, and fine tuned electric fields to achieve their selectivity [17, 18, 20]. The radius of the narrowest part of the channel, known as the selectivity filter, measures only 5-8 Å. The channel interior is unexpectedly hydrophobic, apart from a stripe of polar groups lining the channel in a curve-linear fashion [16]. Therefore, only molecules such as water and urea, which are very small, can enter and pass the channel. Larger molecules have a chance, only if they are flexible enough to adopt a linear shape and align their hydrophobic and polar groups to the hydrophobic surface and hydrogen bonding groups of the protein, respectively, at any time during permeation [17, 20]. A number of linear sugar molecules, such as glycerol, are structurally flexible enough to meet these requirements and can therefore be transported by a subfamily of AQPs, known as aquaglyceroporins. Transport

of sugar molecules also occurs in a highly selective manner: different stereoisomers of the same molecule may show a tenfold difference in their permeability. The simulations performed by the Resource clearly showed that there is a strong correlation between the permeability of the molecule and its ability to maximize the number of its hydrogen bonds to the channel while maintaining its linear structure, particularly at the selectivity filter. Sugar molecules like arabitol, that cannot meet these requirements, are destined to have a much lower permeability and cannot be transported efficiently by the channel [17, 20].

The simulations were the first that relied on the power of the new generation of teraflop computers, the fastest computer available to biomedical researchers in the US. The work represents a prime example of biomedically relevant research that justifies the considerable investment in these new computers[†].

[†] `http://www.psc.edu/science/schulten2002.html`

Forced Detachment of the Protein Complex CD2-CD58

Our immune system protects us from infectious agents such as viruses and bacteria. To do so, the infectious agents as well as infected cells need to be recognized and destroyed. In the case of cells infected by a virus, this is carried out by T-lymphocytes. The recognition is mediated by the interaction between cell surface proteins, making sure that healthy cells are not destroyed by T-lymphocytes. In humans, the recognition of infected cells by T-lymphocytes is believed to be enhanced by the interaction between the T-lymphocyte adhesion receptor CD2 and its ligand CD58 on so-called antigen presenting cells. Although these proteins do not recognize the infectious agent by themselves, they hold the two cells together in a way that specialized proteins on the T-lymphocite surface can examine the surface of the antigen presenting cell in order to "find" evidence of infection [25].

CD2 and CD58 belong to a group of proteins known as "cell adhesion molecules", which mediate contact between cell surfaces in processes such as the immune response described above, but also in tissue formation and cell motion. Like other cell adhesion molecules, CD2 and CD58 are made of immunoglobulin domains. Their extracellular part includes two such domains, the adhesion between the proteins involving only the most external one (Figure 3). Most of the residues in the adhesive interface are charged and distributed in a way that negatively charged residues of one protein in the complex are complemented by positively charged residues of the other [26].

The charge complementarity of the adhesion surfaces determines the specificity of their interaction. This means that CD2 can only be recognized by CD58 because of the complementarity of their surfaces [25,27,28]. The crystal structure of the adhesive complex of CD2 and CD58 [26] shows pairs of complementary charges in the interface bound to each other. Although the importance of these charge pairs for the specificity of the interaction has been clearly established, their contribution to the adhesion strength was not fully understood.

To address the role of complementary charges, the response of the CD2-CD58 complex to an external pulling force was studied using steered molecular dynamics simulations. The analysis of the simulations allowed us to answer two important questions regarding the adhesive function of CD2 and CD58. First, the detachment of CD2 and CD58 does not involve unraveling of domains under physiological conditions [29]. Second, the complementary charge pairs that are responsible for the binding specificity of CD2 and CD58 determine the adhesion strength as well. They separate one by one, and after each such step the distance between the proteins increases by a discrete amount (Figure 3). The order of separation allows one to classify the charge pairs according to their contribution to the adhesion strength. This is determined by the position of the complementary charge pairs relative to the line of action of the applied force. Pairs closer to this line

are non-critical and separate first. Critical ones stay longer and separate during the second half of the simulation period. There is a close correlation between these results and experiments, where adhesion was affected by systematic elimination of complementary charges [27,28]. The close agreement between simulation and experiment suggests that *in vivo*, the detachment may be induced by the relative movement of adhered cells, pulling the complex apart in the same fashion that was done in the simulations. This project is a prime example of a collaboration in which the Resource enhances the efforts of an experimental research group through modeling that guides and analyzes observation.

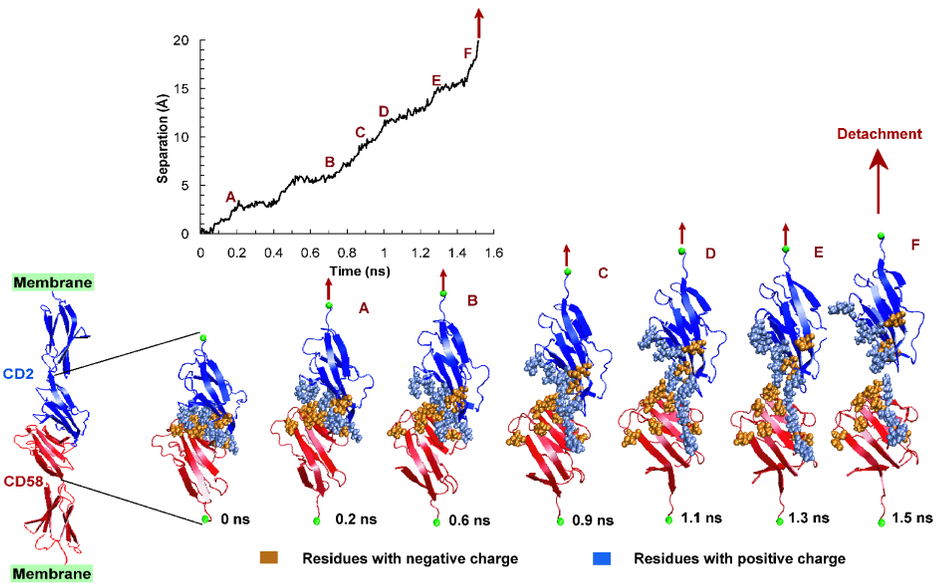

Figure 3: Snapshots of MD simulations illustrating the stepwise detachment of CD2-CD58 complex when subject to a constant force of 400 pN. The inset shows the evolution of the separation in time. These show the sequential rupture of the salt bridges. Charged residues in the binding region are highlighted using VDW representation.

NAMD: Scalable Molecular Dynamics Software

One of the objectives of the resource is to develop molecular dynamics software with extremely high performance on the largest supercomputers available, and to make it available to the broad community. The resource has made excellent progress towards this during the past year. NAMD* is a molecular dynamics software designed for high performance simulation of large biomolecular systems on parallel supercomputers [10]. It builds on the capabilities of the Charm++ parallel programming system.† NAMD attained several new and impressive milestones last year, and earned recognition from the community.

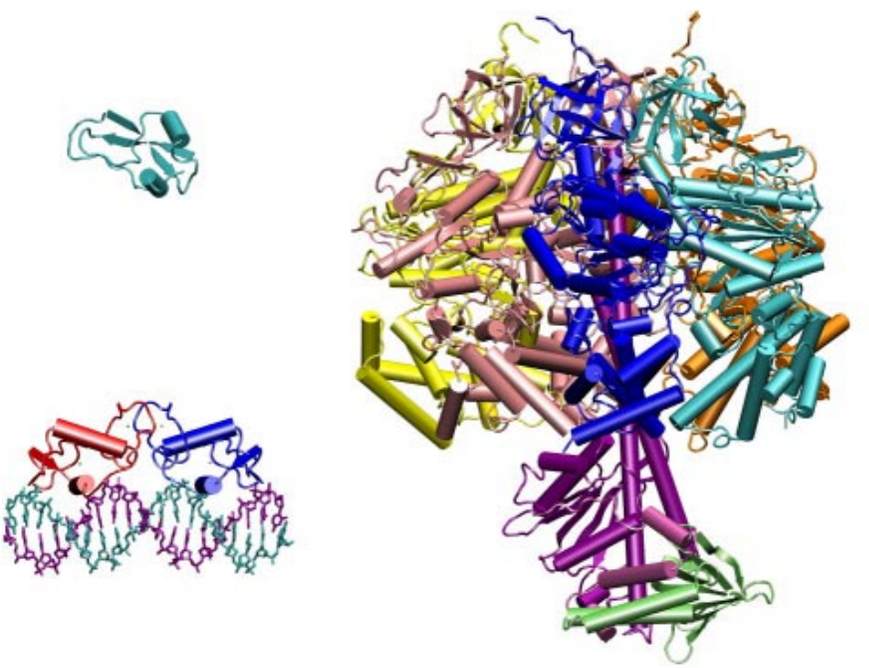

Figure 4: Simulations have increased in size, from bovine pancreatic trypsin inhibitor (upper left, 3K atoms), through the estrogen receptor (lower left, 36K atoms), to F_1-ATPase (right, 327K atoms,). (Atom counts include solvent.)

With continuing increases in high performance computing technology, the domain of biomolecular simulation has rapidly expanded from isolated proteins in solvent to biomolecular complexes in their native environments. Figure 4 compares simulation sizes of well-known biomolecular systems that have been studied by molecular dynamics: bovine pancreatic trypsin inhibitor, the first protein simulated [30], a pair of DNA binding domains of the estrogen receptor complexed with DNA [31], and the F_1 fraction of ATP synthase. Today, simulations of biomolecular systems with over 100,000 atoms lasting 10 ns are

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

†URL: `http://charm.cs.uiuc.edu/`

becoming routine [18] and discoveries of the structures of large biomolecular complexes like the RNA polymerase II [32] or the 70S ribosome complex made from the 30S [33] and 50S [34] subunits forecast simulations involving a million atoms and more. The unique capabilities of NAMD make it one of the few programs that can carry out simulations of such large molecular assemblies and run them fast on supercomputers.

Years of work developing NAMD to employ the nation's fastest supercomputers were recognized at the SC2002 High Performance Networking and Computing Conference in Baltimore with the presentation of a *2002 Gordon Bell Award* for unprecedented performance of a wildly used software which is known to be challenging to parallelize. The winning paper [35] reported challenges and successes in efficiently utilizing 3000 processors for a 327,000 atom simulation of F_1-ATPase using the supercomputer at the Pittsburgh Supercomputing Center.

Our efforts in pushing the limits of performance have also benefited the supercomputing community. While optimizing NAMD performance in preparation for the Gordon Bell competition, we observed that when application iteration times are as small as tens of ms, severe performance obstacles surface. The concrete technical observations led to joint work by us, researchers at National Laboratories and at computer companies, resulting in isolation of the problems, and new guidelines for the users of such supercomputers.

In December 2002, NAMD achieved a performance of 1 Teraflop/s on a 327,000 atom cutoff simulation using 3000 processors, an increase of 27% over the performance reported in [35]. The average simulation time per timestep is around 12 ms. This is noteworthy because IBM's Blue Gene project, announced two years ago, aimed at using hundred thousand to million processors to carry out a 32,000 atoms simulation at the pace of 1 ms per timestep.

NAMD, and its sister visualization program VMD[‡], have helped researchers at the Resource discern how muscles stretch, how nerves sense pressure, and how kidneys filter water. NAMD and VMD are distributed, free of charge, to thousands of scientists in industry and academia around the world, quickening the pace of drug discovery and other vital research to unravel biological processes. NAMD has recently enabled a record-breaking two million atom 5 ns simulation of the ribosome running on 768 processors at the Los Alamos National Laboratory, while the large system trajectory analysis features of VMD made it the clear choice for analyzing the respective results.

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

Subprojects

BTA UNIT: C, T

TITLE: Molecular Mechanisms of Energy Conversion in Cells: 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: 89

INVEST1: Ilya Balabin
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Aleksei Aksimentiev
DEGREE2: Ph.D.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: Barry Isralewitz
DEGREE3: M.A.
DEPT3: Biophysics
NONHOST3:

INVEST4: Markus Dittrich
DEGREE4: M.A.
DEPT4: Physics
NONHOST4:

INVEST5: Chalermpol Kanchanawarin
DEGREE5: M.Phys.
DEPT5: Physics
NONHOST5:

INVEST6: Robert Fillingame
DEGREE6: Ph.D.
DEPT6: Biomolecular Chemistry
NONHOST6: University of Wisconsin, Madison

% BTA $: 2 %

ABSTRACT: ABSTRACT

F_1F_o-ATP synthase* is a large protein complex that efficiently converts a transmembrane electrochemical potential into chemical energy by synthesizing ATP from ADP and P_i. For this purpose the protein couples two molecular rotary motors, F_o and F_1, through an elastic central stalk. F_o is a membrane-embedded protein complex that converts the electrochemical potential across the membrane into rotation of the γ-stalk. The solvent-exposed F_1 unit undergoes cyclic conformational transitions which are driven by rotation of the stalk and which cause ATP to be synthesized. The protein can also work efficiently in reverse. In humans F_1F_o ATP synthase is responsible for synthesizing a person's body weight in ATP per day, thereby fueling most metabolic processes.

F_o unit. The mechanism of torque generation in F_o was investigated by linking a stochastic model capable of describing processes on a millisecond time scale to nanosecond molecular dynamics simulations [7]. Using the program NAMD [10], the molecular dynamics simulations were performed on a system of 111,714 atoms that included a ring of ten *c* subunits (rotor), a four helix bundle of subunit *a* (stator), a 112×123 Å^2 patch of phosphatidylethanolamine membrane, and $20,554$ water molecules. In the stochastic model, the state of the system is 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 *a* and *c* subunits was observed; transfer of the 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. The emerging mechanism of F_o operation [7] extends the model proposed earlier [8, 36, 37] by our collaborator R.H. Fillingame.

The same F_o model has been used to investigate the proton pathway employing molecular dynamics simulations with NAMD [10]. The polar side groups and water molecules buried inside the system were found to form two proton half-channels, supporting recent experiments by R.H. Fillingame [38]. Combining these findings with our analysis of subunit cross-linking experiments [39, 40], we propose a rotary

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

mechanism which suggests how a proton is translocated through F_o. Our future work will focus on the mechanism of force generation in F_o.

F_1 unit. To examine how F_1-ATP synthase converts a torque applied to its central stalk into formation of chemical bonds at binding sites 100 Å away, we have used NAMD [10] to perform molecular dynamics simulations on a 327,000 atom system consisting of the F_1 protein complex, nucleotides, water, and ions [9]. Steered molecular dynamics studies, forcing the base of the central stalk to rotate at 24 °/ns were carried out to examine details of the process. At around 72 ° of rotation, several events consistent with synthesis were observed. They included an increase in total torque required to continue rotation, hinge motions of β subunits, central stalk–β subunit cooperative interactions, ATP unbinding at the β_{TP} catalytic site, and rebinding of a key arginine residue at the same site. The coiled-coiled stalk helices exhibited winding that may play a role in inducing active site changes.

The Resource has also performed *ab initio* quantum mechanical/molecular mechanical calculations of ATP hydrolysis in the β_{TP} binding pocket of F_1-ATPase [11]. The modeled system contained 8,378 atoms, 61 of which were treated quantum mechanically. We were able to characterize the reaction path of the catalytic event, its energetics and important interactions of the reactive core with the protein environment. Our simulations suggest that the energetically dominant pathway proceeds via a multi-center proton transfer mechanism. ATP hydrolysis in β_{TP} was found to be endothermic, thereby facilitating ATP synthesis inside the catalytic site rather than promoting ATP hydrolysis. Future investigations will study ATP hydrolysis in the β_{DP} binding site to better understand conformational and energetic changes along the catalytic cycle.

BTA UNIT: C

TITLE: Aquaporins

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

AXIS I: 2

AXIS II: 74h,89

INVEST1: Emad Tajkhorshid
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Fangqiang Zhu
DEGREE2: M.S.
DEPT2: Physics
NONHOST2:

INVEST3: Deyu Lu
DEGREE3: M.S.
DEPT3: Physics
NONHOST3:

INVEST4: Paul Grayson
DEGREE4: S.B.
DEPT4: Physics
NONHOST4:

INVEST5: Morten Jensen
DEGREE5: Ph.D.
DEPT5: Department of Physics
NONHOST5: Technical University of Denmark

INVEST6: Robert Stroud
DEGREE6: Ph.D.
DEPT6: Department of Biochemistry and Biophysics
NONHOST6: University of California at San Francisco

% BTA $: 1 %

ABSTRACT: Aquaporins (AQPs)* are a family of membrane proteins that mediate fast transport of large volumes of water across biological membranes. In addition to water, some members of the family, known as aquaglyceroporins, allow other neutral molecules, such as linear sugar molecules and urea, to permeate [12,41]. Charged species, however, cannot permeate water pores of AQPs. Particularly interesting is that even protons, which can be transported through hydrogen bonded chains of water, are also efficiently blocked [42]. Impaired function of AQPs is associated with pathophysiological conditions, such as *diabetes insipidus* [12] and congenital cataracts. High resolution structures of two AQPs, the mammalian aquaporin-1 (AQP1) and the *E. coli* glycerol uptake facilitator (GlpF), have been determined [43–45].

AQP1 [45] and GlpF [44] were simulated in fully solvated lipid bilayers, consisting of about 100,000 atoms, that are required for the study of natural function of the channels. The systems were simulated using molecular dynamics for several nanoseconds, and permeation and structure of water inside the channels were investigated and compared in the two channels. During the simulations, water molecules pass through the channel in single file. The movement of water molecules through the channel is concerted, and can be described by a continuous–time random–walk model [24]. The integrity of the single file remains intact during the permeation indicating that a disrupted water chain cannot be the basis for the mechanism of proton exclusion in aquaporins. Detailed analysis of the dynamics of water inside the channel revealed a novel mechanism by which AQPs can effectively block protons, while permitting fast water transport [18]. The simulations showed that the arrangement of water molecules in the channel is highly ordered and highly unfavorable for proton transport [18]. Water-water electrostatic interactions are in all regions inside the channel stronger than water-protein interactions, except near a conserved, positively charged Arg residue . We find that variations of the protein electrostatic field through the channel, owing to preserved structural features, completely explain the strongly enforced water orientation. Furthermore, permeation of a cation is prevented by ion-protein electrostatic interactions at the conserved NPA motifs [24].

In order to compute the osmotic permeability of AQPs, we applied a hydrostatic pressure difference across a membrane in molecular dynamics simulations [15]. The method, which is based on application of small forces on individual water molecules in bulk regions along the desired direction of permeation, was applied to an AQP1 tetramer. Four such simulations (each lasting 5 ns) were performed at different

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

pressure differences. The osmotic permeability was then calculated from the flux-pressure relationship and found to agree well with experimental observations. Comparison of permeabilities in GlpF and AQP1 indicates that water permeation is faster in GlpF, which is consistent with the wider size of the water pore in this channel.

The efficiency of GlpF for glycerol uptake is crucial for the cell to survive at low sugar concentrations. Although GlpF allows both influx and efflux of glycerol, its structure exhibits a significant degree of asymmetry. The potential of mean force characterizing glycerol in the channel shows a corresponding asymmetry with an attractive vestibule only at the periplasmic side [17]. Analysis of the potential of mean force showed that the channel kinetics can be captured by a six-step model, yielding a conductance that agrees well with observation [46]. The presence of an attractive vestibule at the periplasmic side of the channel increases the conductance rate of glycerol by 40% and 75% at 10 μM and 10 mM extracellular glycerol concentrations, respectively. It was also found that GlpF is able to release glycerol as rapidly as it can take it up, and the efficiency is the same for uptake and release [46].

BTA UNIT: C

TITLE: Forced Detachment of the Protein Complex CD2-CD58

KEYWORDS: Steered molecular dynamics, Cell adhesion molecules, CD2, CD58

AXIS I: 1a, 6

AXIS II: 64, 89

INVEST1: Marco V. Bayas
DEGREE1: M. S.
DEPT1: Center for Biophysics and Computational Biology
NONHOST1:

INVEST2: Deborah Leckband
DEGREE2: Ph. D., Professor
DEPT2: Chemical Engineering and Bioengineering
NONHOST2:

% BTA $: 1 %

ABSTRACT: Steered Molecular Dynamics simulations have been used to study the response of the adhesion protein complex CD2-CD58 to a pulling force*. The force was applied along the line joining the backbone carbon atoms in the c-terminus of each protein. It is likely that this is the direction of the forces applied to the complex *in vivo* through the motion of the interacting cells, T-lymphocite and antigen presenting cells. The simulations were performed at both constant pulling velocity and constant pulling force. The constant velocity simulations show that the system can respond to an external force by two mechanisms that depend on the loading rate. At rapid loading rates of 70 and 35 pN/ps (pulling speeds of 1 and 0.5 Å/ps) the proteins unfold before they separate, whereas at slower loading rates of 7 and 3.5 pN/ps (pulling speeds of 0.1 and 0.05 Å/ps), the proteins separate before the domains can unfold. These simulations also showed that the unraveling starts when the magnitude of the force is greater than 500 pN. Consistently, when the system was pulled with a constant force of 400 pN, the two proteins separated without significant structural distortion. These findings suggest that, *in vivo*, protein unfolding is not coupled to the adhesive function of CD2 and CD58. The simulations further confirm that interdomain salt-bridges primarily determine the tensile strength of the protein-protein bond. The separation between the proteins increases substantially

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

only after a salt-bridge is broken. Also, the order of salt-bridge rupture depends mainly on the positions of the bonds relative to the line of action of the applied force; salt bridges close to this line break first. The importance of each salt-bridge for adhesion, determined from the simulations, correlates closely with their role in cell-cell adhesion and equilibrium binding determined by site directed mutagenesis experiments.

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: Robert Skeel
DEGREE1: Ph.D.
DEPT1: Computer Science
NONHOST1:

INVEST2: Laxmikant Kale
DEGREE2: Ph.D.
DEPT2: Computer Science
NONHOST2:

INVEST3: James Phillips
DEGREE3: Ph.D.
DEPT3: Beckman Institute
NONHOST3:

INVEST4: Jay DeSouza
DEGREE4: M.S.
DEPT4: Computer Science
NONHOST4:

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

INVEST6: Gengbin Zheng
DEGREE6: M.S.
DEPT6: Computer Science
NONHOST6:

% BTA $: 15 %

ABSTRACT: NAMD* is a parallel molecular dynamics code designed for high performance simulation of large biomolecular systems [10]. 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.

Development in the past year has focussed on extracting the maximum serial and parallel performance possible from the NAMD 2 design while maintaining a stable production system for our users. New enhancements include:

- Parallel scalability has been greatly improved on 1000+ processors.
- Constant pressure simulation methods have been improved.
- Serial NAMD kernel benchmark developed and submitted to SPEC-CPU 2004.
- Serial performance has been improved on Itanium via inner loop tuning.
- Serial performance has been improved on all platforms via new pairlists.
- Requirements analysis and initial design of NAMD 3 is underway.

The final major release of the NAMD 2 series, version 2.5, is scheduled for May 2003. Resource personnel received a *2002 Gordon Bell Award* for a paper [35] reporting successes and challenges in scaling NAMD for a 327,000 atom simulation of F_1-ATPase on the 3000 processor *Lemieux* HP AlphaServer cluster at the Pittsburgh Supercomputing Center. In December 2002, after further tuning in collaboration with HP and PSC, NAMD achieved a performance of 1 Teraflops on Lemieux for this system. Beyond the Resource, NAMD has recently enabled a record-breaking two million atom 5 ns simulation of the ribosome running on 768 processors of the Los Alamos ASCI Q machine (K. Sanbonmatsu, Los Alamos National Lab, private communication). Future work will concentrate exclusively on a redesigned NAMD, NAMD 3, which will allow a wider variety of simulation methods to be implemented and more easily maintained, while preserving and extending the parallel scalability of NAMD 2. Initial release of NAMD3 is scheduled for December 2003.

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

†URL: `http://charm.cs.uiuc.edu/`

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: John Stone
DEGREE1: M.S.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Justin Gullingsrud
DEGREE2: B.A.
DEPT2: Department of Physics
NONHOST2:

INVEST3: Eamon Caddigan
DEGREE3: Undergrad
DEPT3: Computer Engineering
NONHOST3:

% BTA $: 11 %

ABSTRACT: VMD [47] 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 run within the native windowing system and OpenGL acceleration provided by MacOS X. Macintosh users can now use VMD's visualization features to full effect. The entire VMD graphical user interface has been rewritten from the ground up, emphasizing ease of use, task efficiency, and better suitability for laptops. Molecular dynamics trajectories can now

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

be "smoothed" on-the-fly, filtering out transient thermal fluctuations, yet allowing researchers to observe slower conformational changes that contribute to molecular function. Further enhancements have been made to ease the creation of movies for presentations and web sites with the built-in "vmdmovie" plugin.

VMD 1.8 was released in December 2002. More than 6,200 unique users have registered and downloaded VMD 1.8, over 1,200 of whom are NIH-funded researchers. VMD 1.8.1 is expected to be released by May 2003.

Future VMD development will improve the quality of molecular representations, movie making features, support for multiple graphics windows and viewports, and will further pursue plugin interfaces to third-party software packages and databases.

BTA UNIT: T, D, S

TITLE: BioCoRE Development

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

AXIS I: 9

AXIS II: 42, 51, 89

INVEST1: Gila Budescu
DEGREE1: Ph. D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Laxmikant V. Kalé
DEGREE2: Ph. D.
DEPT2: Computer Science
NONHOST2:

INVEST3: Robert Brunner
DEGREE3: B. S.
DEPT3: Beckman Institute
NONHOST3:

INVEST4: Kirby Vandivort
DEGREE4: M. S.
DEPT4: Beckman Institute
NONHOST4:

INVEST5: Michael Bach
DEGREE5: B. S.
DEPT5: Beckman Institute
NONHOST5:

INVEST6: David Brandon
DEGREE6: M. S.
DEPT6: Speech Communication
NONHOST6:

INVEST7: Rosemary Braun
DEGREE7: B. Sc.
DEPT7: Physics
NONHOST7:

INVEST8: Derek Dagit
DEGREE8: Undergraduate
DEPT8: Computer Science
NONHOST8:

INVEST9: Sameer Kumar
DEGREE9: M. S.
DEPT9: Computer Science
NONHOST9:

INVEST10: Mani Potnuru
DEGREE10: B. Tech.
DEPT10: Computer Science
NONHOST10:

INVEST11: Elizabeth Villa
DEGREE11: B. S.
DEPT11: Center for Biophysics and Computational Biology
NONHOST11:

% BTA $: 20 %

ABSTRACT: BioCoRE [48] is a web-based collaborative environment designed to enhance biomedical research and training. By using a standard web-browser (on a desktop or laptop computer or handheld PDA) scientists create projects in which all private data is secure and is shared only within the specific project team. 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 regularly inform the project team of the project status. BioCoRE sessions are automatically recorded and can be reviewed later by all project team members. A built-in evaluation component provides systematic and continuous user feedback,* and is described in the next subproject.

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

Major BioCoRE developments in the past year include the ability to create *public* project areas which enable information sharing on a scale beyond project teams. A new lab book tracks research progress, and WebDAV support is now available for the shared filesystem. BioCoRE has begun this year to operate as a training platform embracing the development of training modules and materials.

Finally the BioCoRE server source code has been released recently and has been installed at the NCSA supercomputer center to be used by the NCSA users. BioCoRE installation requests are increasing and the interest in local BioCoRE servers is growing.

Future BioCoRE efforts will focus on additional integration of biomedical applications, further development of the training arena, and on increased adoption of BioCoRE by the community.

BTA UNIT: D, S

TITLE: BioCoRE Evaluation

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

AXIS I: 9

AXIS II: 42, 51, 89

INVEST1: Gila Budescu
DEGREE1: Ph. D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: David Brandon
DEGREE2: M. S.
DEPT2: Speech Communication
NONHOST2:

% BTA $: 2 %

ABSTRACT: The BioCoRE evaluation is a built-in component of the environment. The activities of the BioCoRE evaluation team over the last year fall included conceptual development, data collection, and prototype creation. To provide a context for evaluation data, a multi-theoretical overview applying several technology assessment theories to BioCoRE was produced following reviews of the utility of each model with the development team. Several measures utilizing unobtrusive data collected by BioCoRE were developed to describe user behavior (individually, within projects, and across BioCoRE) and tool access in terms of gross use, gross use over time, distribution of use, and distribution of use over time. More data collection was accomplished via the BioCoRE 2002 user survey, in which registered users were asked to complete a web-based survey collecting, basic user data, responses to questions based on usability concepts, and reactions to open questions. In response to prior evaluation data, the evaluation team produced a web-based prototype of the BioCoRE Job Management Tool that incorporates features desired by users such as jobs based on prior jobs, sequential job submission, editable scripts, and easier views of job data. The BioCoRE Notebook is also a focus of prototype development, with a File Management Notebook component in early development as a complement to the successfully prototyped Presentation Notebook component.

BTA UNIT: C

TITLE: Mechanobiology

KEYWORDS: titin, fibronectin, protein unfolding, intermediate, steered molecular dynamics

AXIS I: 13,20

AXIS II: 74h

INVEST1: Mu Gao
DEGREE1: M.S.
DEPT1: Physics
NONHOST1:

INVEST2: Hui Lu
DEGREE2: Ph. D.
DEPT2: Department of Bioengineering
NONHOST2: University of Illinois at Chicago

INVEST3: Matthias Wilmanns
DEGREE3: Ph. D.
DEPT3:
NONHOST3: EMBL Hamburg Outstation

INVEST4: Viola Vogel
DEGREE4: Ph. D.
DEPT4: Department of Bioengineering
NONHOST4: Univeristy of Washington

% BTA $: 2 %

ABSTRACT: The elasticity of mechanical proteins is essential for cell function. Two examples are the muscle protein titin* responsible for developing passive elasticity and extensibility in muscle, and the extracellular matrix protein fibronectin† forming fibrils that attach cells to substrates and guide cell movements. The mechanical properties of titin/fibronectin modules, namely immunoglobulin-like (Ig) domains and fibronectin type III (FN-III) modules, have been studied by using atomic force microscopy (AFM) [49, 50]. Complementary to AFM experiments, over the past five

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

†URL: `http://www.ks.uiuc.edu/Research/fibronectin/`

years we have successfully studied, at the atomic level, the mechanical responses of titin/fibronectin modules using steered molecular dynamics (SMD) simulations with the program NAMD [51–59] (reviewed in [60–62]).

Previous SMD studies of titin domains had been restricted to I27. We have extended our SMD study to titin domain I1 [63]. The atomic structure of I1 was determined at 2.1 Å by our collaborator Matthias Wilmanns [64]. For our study we built an explicit solvent model by solvating the structure in a water sphere (18,000 atoms), followed by performing SMD unfolding simulations with both constant velocity and constant force protocols. The mechanical unfolding forces have been applied to oxidized I1, which has a disulfide bond between its two β-sheets, as well as to reduced I1 in which the disulfide bond is absent. The simulations reveal that I1 is protected against external stress mainly through six inter-strand hydrogen bonds between its A and B β-strands. The disulfide bond enhances the mechanical stability of oxidized I1 domains by restricting the rupture of backbone hydrogen bonds between the A′- and G-strands. The disulfide bond also limits the maximum extension of I1 to ∼220 Å.

Experimental studies have indicated that FN-III modules undergo reversible unfolding as a mechanism of elasticity. The unfolding of FN-III modules, including the cell binding FN-III$_{10}$ module, has further been suggested to be functionally relevant by exposing buried cryptic sites or modulating cell binding. Continuing a long-standing collaboration with the Vogel group of University of Washington, we have built an extended periodic box (126,000 atoms) to probe the unfolding of FN-III$_{10}$ for extensions longer than 60 Å [65]. Three meta-stable intermediates were identified in SMD stretching simulations. The protein transits to the first and the second intermediates within 30 Å of stretching, the intermediates corresponding to a twisted and an aligned state prior to unraveling FN-III$_{10}$'s β-strands. A third intermediate, at an extension of ∼100 Å, follows unraveling of FN-III$_{10}$'s A- and B-strands and precedes breaking of inter-strand hydrogen bonds between F- and G-strands. The simulations also revealed three forced unfolding pathways of FN-III$_{10}$, one of which is preferentially selected under physiological conditions. Similar intermediates have also been recently identified in simulations of FN-III$_1$ [66]. The mechanical stability of nine different FN-III modules has been compared to develop an understanding of the design and heterogeneity of fibronectin domains used in the extracellular matrix [67].

BTA UNIT: T

TITLE: MscL and MscS Gating Mechanisms

KEYWORDS: MscL, MscS, mechanosensitive, membrane protein

AXIS I: 2,7a

AXIS II: 74f,h;77

INVEST1: Justin Gullingsrud
DEGREE1: B.A
DEPT1: Physics
NONHOST1:

INVEST2: Marcos Sotomayor
DEGREE2: M.S
DEPT2: Physics
NONHOST2:

% BTA $: 5 %

ABSTRACT: Mechanosensitive channels* are integral membrane proteins that play an important physiological role in living cells. In prokaryotes, these channels are activated by mechanical stress in the membrane, providing a controlled response to the osmolality of the environment and preventing cell bursting. A crystal structure of one of these channels, MscL from *M. tuberculosis* (Tb-MscL) [68], shows it in its closed form, leaving the structure of the open channel and the gating pathway unresolved.

A report of SMD simulations of MscL investigating how forces arising from membrane tension induce gating of the channel has recently been completed. In this work, NAMD was used to simulate MscL in a bath of water, with external forces provided to simulate the effect of membrane stretch. For the first time, the depth-dependent surface tension of the bilayer calculated from all-atom simulations [69] was used to model the interaction of the bilayer with the channel. Using these modeled forces, a fully expanded state was obtained on the 10 ns time scale. The simulation agreed well with proposed models of MscL gating, in that it entails an iris-like expansion of the pore accompanied by tilting of the transmembrane helices. It also showed that the channel was most easily opened when force was applied predominantly on the cytoplasmic side of MscL. Comparison of simulations in which

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

gating progressed to varying degrees identified components that determine the tension threshold of the channel.

The recent characterization of the structure of another mechanosensitive channel, MscS from *E. coli* [70], in a possibly open state, is very exciting, as it provides a new view of stretch-activated gating. Perhaps even more interesting, MscS is the first crystallographically-resolved voltage-gated channel. This gives the opportunity to study voltage-mediated gating mechanisms and coupling between tension and voltage sensitivities. Studies of MscS in the Resource have been initiated; the large size of the channel (27,800 atoms in the protein alone) and the need to study the channel in its native membrane environment will require simulations of MscS that use significant computational resources.

BTA UNIT: T, C

TITLE: Multi-scale Molecular Modeling of the lac Repressor-DNA Complex

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
DEGREE1: Ph.D.
DEPT1:
NONHOST1: IBM T.J. Watson Research Center

INVEST2: L. Mahadevan
DEGREE2: Ph.D., Professor
DEPT2: Applied Mathematics and Theoretical Physics
NONHOST2: University of Cambridge, UK

INVEST3: Elizabeth Villa
DEGREE3: B.S.
DEPT3: Center for Biophysics and Computational Biology
NONHOST3:

% BTA $: 2 %

ABSTRACT: Protein-DNA interactions are responsible for a class of fundamental processes of life: the storage and expression of genetic information. Modeling of these interactions can contribute greatly to our understanding of the mechanisms of life, and could result in revolutionary developments in medicine. 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. All-atom computer simulation of the complex is unfeasible for such large systems. For example, DNA loops several hundred nanometers long may form when a single protein (typically, the size of several nanometers) binds simultaneously to two distant DNA sites, yielding systems with millions of atoms. The Resource has developed a multi-scale approach to connect microscopic simulations of protein and DNA with continuum-level descriptions of DNA loops*. During the past funding year, the

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

Resource has further developed the multi-scale methodology. The method builds coarse-grained models of long DNA loops in order to determine the structure, energy, and the forces arising in protein-DNA interaction. It is based on the theory of elasticity and takes into account the bending anisotropy and electrostatics of DNA [71, 72]. The forces obtained by this elastic rod approach are incorporated in fully atomistic molecular dynamics simulations of the DNA binding proteins based on the steered molecular dynamics approach. The loop itself is not explicitly included in the simulations. Repetitive rounds of steered molecular dynamics are alternated with recomputing the elastic force to account for the changes in the force arising from changes in the protein-DNA structure. The described method was applied to the *lac* repressor-DNA complex. The all-atom model of the complex was built using available X-Ray and NMR structures, none of which, however, included a long (76 or 384 bp) DNA loop, which the protein is known to induce in the E. coli genome. The structure was hydrated using VMD, yielding a system with a total size of more than 230,000 atoms and equilibrated for 1.8 ns using the molecular dynamics program NAMD. The coarse-grained structure of the missing loop was modeled and was found to exert an elastic resistance of $\sim$10 pN. The multi-scale simulation with the force is being performed recursively as stated above on 512 Alpha processors at the Pittsburgh Supercomputing Center. So far, simulations have covered a 5 ns time period. The resulting data will allow us to compare the computed protein-DNA complex with available crystal structures. The simulations will reveal the degrees of freedom of the protein. The structure of the lac repressor-DNA complex resulting from these simulations will presumably be closer to the *in vivo* protein-DNA complex than the X-ray structure obtained in the absence of the clamped DNA loop.

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,h;77;89

INVEST1: Rosemary Braun
DEGREE1: B.Sc.
DEPT1: Physics
NONHOST1:

INVEST2: Justin Gullingsrud
DEGREE2: B.A.
DEPT2: Physics
NONHOST2:

INVEST3: Donald M. Engelman
DEGREE3: Ph.D.
DEPT3: Dept. Molecular Biophysics and Biochemistry
NONHOST3: Yale

% BTA $: 2 %

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 [73–75]. 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.

Molecular dynamics simulations of sodium dodecyl sulfate (SDS) and the human glycophorin-A (GpA) transmembrane dimer provide an atomic-level depiction of the dynamics of micelle aggregation and helix association. The initial configuration of the system consisted of the GpA NMR structure surrounded by water and 58

randomly placed SDS molecules, corresponding to 0.14M SDS concentration. Simulations of the 65,000 atom system were carried out over 24 ns in the NpT ensemble with PME electrostatics using the molecular dynamics code NAMD [10]. The long simulation time allows one to observe spontaneous aggregation of SDS into a micelle partially enveloping the protein helices. Individual SDS molecules diffused with $D = 1.2 \cdot 10^{-3}$ nm^2/ps, forming a small micelle comprising 24 SDS molecules around GpA by the end of 19 ns. Instability of the hydrophobic GpA helices in water is resolved after being partially surrounded by SDS at 9.5 ns.

BTA UNIT: T

TITLE: IMD: Interactive Molecular Dynamics

KEYWORDS: molecular dynamics, molecular visualization, haptic feedback, IMD

AXIS I: 9

AXIS II: 42, 89

INVEST1: Jordi Cohen
DEGREE1: M.Sc.
DEPT1: Department of Physics
NONHOST1:

INVEST2: Paul Grayson
DEGREE2: B.Sc.
DEPT2: Department of Physics
NONHOST2:

INVEST3: Justin Gullingsrud
DEGREE3: B.A.
DEPT3: Department of Physics
NONHOST3:

INVEST4: John Stone
DEGREE4: M.Sc.
DEPT4: Beckman Institute
NONHOST4:

INVEST5: Emad Tajkhorshid
DEGREE5: Ph.D.
DEPT5: Beckman Institute
NONHOST5:

% BTA $: 5 %

ABSTRACT: Interactive molecular dynamics* (IMD) [23] is a novel computational methodology that enables researchers to interact with their simulations. By means of a force-feedback haptic device, a researcher can apply external forces to atoms or groups of atoms in a running simulation. The process is made interactive by the fact that the dynamics of the system can be monitored in real-time through a visualization program (*e.g.,* VMD [47]), and by the fact that the researcher also gets an immediate visual and motor response from his actions on the system through the use of a mechanical input/output device. IMD is frequently used to accelerate slow or complex events, such as docking, the transport of molecules through channels, and the placement of compounds during system-building. It is also an ideal investigative tool that provides a useful method for developing and testing hypotheses about the function of biomolecular systems prior to running expensive simulations.

We have developed a tool – which we call AutoIMD – for quickly setting up interactive molecular dynamics simulations from within VMD, without the need to manually setting up the required files. AutoIMD permits a researcher to instantaneously visualize and interact with the evolution of an arbitrary part of his or her system given only the initial coordinates and structure. AutoIMD achieves this by building a reduced system containing the atoms of interest, along with a fixed scaffold around them. It takes care of generating all the required simulation input, of running and connecting to a NAMD [10] simulation (remotely or locally), and of merging the new coordinates back into the larger structure. This tremendously facilitates the micro-manipulation of individual residues, the interactive placement of small compounds, and the scientific investigation of processes on the fly, all with very light computational requirements. AutoIMD is now included as a package within VMD.

In order to study physical mechanisms underlying the selectivity of the *E. coli* glycerol uptake facilitator GlpF, we used IMD to investigate the permeation of two linear sugar molecules, ribitol and arabitol [20]. These molecules are stereoisomers, i.e., they both include the same number of hydroxymethyl groups in their structures, and differ only with regard to the position of one of the hydroxyl groups along the chain. However, they show a tenfold difference in their permeation rate through GlpF [44]. Using IMD, the molecules were positioned at different regions of the channel, and the conformation of their chemical groups was manipulated to optimize their interaction with the channel. Favorable configurations found in this manner were simulated using equilibrium molecular dynamics simulations. IMD results revealed that, during its permeation, ribitol is able to maintain its hydrophobic interaction with the channel interior, while aligning all of its hydroxyl groups to

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

hydrogen bonding sites of the channel. The structure of arabitol, however, was found to be incapable of such interactions at the selectivity filter of the channel, thus its lower permeation rate [20]. A combination of induced geometrical fit and optimal hydrogen bonding is responsible for the high stereoselectivity of GlpF. Furthermore, an induced rapid dipole moment reversal was observed for both ribitol and arabitol as they pass the center of the channel, and competition for hydrogen bonding sites with water in both cases was critical for substrate motion.

BTA UNIT: T

TITLE: Permeation and Gating in the ClC Chloride Channel

KEYWORDS: chloride channel, ion channel, permeation, gating, umbrella sampling, potential of mean force

AXIS I: 2, 20, 27

AXIS II: 74h, 77, 84

INVEST1: Jordi Cohen
DEGREE1: M.Sc.
DEPT1: Department of Physics
NONHOST1:

% BTA $: 1 %

ABSTRACT: The ClC chloride channels constitute an ancient gene family of anion-selective voltage-gated channels. So far, we know of nine ClC homologs in mammals, which account for a wide range of functions such as the control of membrane excitability in skeletal muscle cells, the regulation of cell volume and organelle acidity, and trans-epithelial transport in the kidneys, to name a few [76]. In humans, inherited mutations of ClCs cause myotonia congenita, Dent's disease and Bartter's syndrome. The crystallization of two bacterial ClCs in 2002 [77] provided the world with a second known ion channel structure (after the potassium channel), paving the way to a detailed understanding of ion channel permeation and of the peculiar properties of ClC ion currents such as its unusual coupling between permeation and gating [78, 79].

We are well on our way to answering many aspects of the ClC permeation mechanism and its "fast" voltage gate. To do this, we have equilibrated a 97,000-atom protein in a membrane system under NPT conditions. We have then proceeded to perform umbrella sampling simulations on 40,000-atom subsets under NVT conditions for a total of 30ns using NAMD [10]. Our efforts so far have focused on two properties of the channel. On one hand, we are investigating the energies of the different conformations of a pair of oppositely charged residues (E148 and R147) at the extra-cellular entrance of the pore. We find that residues act like a gate by blocking and unblocking the pore in response to changes in voltage (which translate in shifts of the energy landscape). On the other hand, we are constructing a full description of the 2- and 3-ion potential of mean force for Cl^- permeation through the pore. In both cases, the potentials of mean force give information about all

the energy barriers and the equilibrium rates of transitions between all configurations and provide the necessary starting point for further theoretical work aimed at understanding the current-voltage relationships in the ClC channel.

BTA UNIT: T

TITLE: Calculating Free Energy from Steered Molecular Dynamics Simulations

KEYWORDS: free energy calculation, potential of mean force, steered molecular dynamics, Jarzynski's equality, helix-coil transition, polyalanine, umbrella sampling

AXIS I: 9

AXIS II: 84, 89

INVEST1: Sanghyun Park
DEGREE1: M.S.
DEPT1: Physics
NONHOST1:

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

INVEST3: Emad Tajkhorshid
DEGREE3: Ph.D.
DEPT3: Beckman Institute
NONHOST3:

% BTA $: 3 %

ABSTRACT: Steered molecular dynamics* is a powerful technique to investigate structures and functions of biomolecules in computer simulations [60]. Using steered molecular dynamics, researchers can focus on important aspects of their systems, minimizing the computational cost. While steered molecular dynamics 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 steered molecular dynamics simulations. A process simulated with steered molecular dynamics is intrinsically in nonequilibrium, whereas free energy is an equilibrium quantity. Jarzynski's equality provides a way to extract equilibrium information from nonequilibrium processes [80].

Recently, the Resource carried out a benchmark study on the free energy calculation from steered molecular dynamics simulations [81]. The helix-coil transition of the

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

10-alanine polypeptide was used as an exemplary system. The molecule is small enough (104 atoms) to permit systematic study, yet complex enough to be considered a prototype of biomolecular systems. In a steered molecular dynamics simulation performed with NAMD [10], 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. We found that the efficiencies of our method and umbrella sampling are comparable.

BTA UNIT: C, T

TITLE: Retinal Proteins

KEYWORDS: rhodopsin, purple membrane, early intermediates, spectral tuning

AXIS I: 7a, 25b

AXIS II: 74h, 89

INVEST1: Shigehiko Hayashi
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Emad Tajkhorshid
DEGREE2: Ph.D.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: Jan Saam
DEGREE3: M.S.
DEPT3: Institut für Biologie
NONHOST3: Humboldt Universität Berlin

INVEST4: Ehud M. Landau
DEGREE4: Ph.D.
DEPT4: Department of Physiology and Biophysics, and The Membrane Protein Laboratory
NONHOST4: The University of Texas Medical Branch

INVEST5: Sándor Suhai
DEGREE5: Ph.D.
DEPT5: Department of Molecular Biophysics
NONHOST5: German Cancer Research Center

INVEST6: Mordechai Sheves
DEGREE6: Ph.D.
DEPT6: Organic Chemistry
NONHOST6: Weizmann Institute of Science

INVEST7: Hideki Kandori

DEGREE7: Ph.D.

DEPT7: Department of Applied Chemistry

NONHOST7: Nagoya Institute of Technology

INVEST8: Massimo Olivucci

DEGREE8: Ph.D.

DEPT8: Dipartimento di Chimica

NONHOST8: Universita di Siena

% BTA $: 2 %

ABSTRACT: Retinal proteins, or rhodopsins, are membrane receptors that are employed by a wide spectrum of living cells to detect ambient light in a highly selective manner, and to use its energy to trigger different cellular responses. In some rhodopsins, such as the archaebacterial proton pump bacteriorhodpsin (bR)*, special structural designs enable the protein to convert light energy to chemical form, which can be stored and used later by the cell; others, e.g., the visual receptor of the eye rhodopsin†, via coupling to cell signaling pathways, translate the external light signal to a biochemical signal inside the cell, which is further processed by the organism, furnishing such important sensory capabilities as vision and phototaxis. In all rhodopsins, detection and absorption of light are accomplished by a polyene chromophore, retinal, whose maximal absorption is largely controlled by the protein matrix through a manifold of steric and electrostatic interactions. The absorption of light by retinal induces a highly selective isomerization around one of the double bonds, which in turn triggers the receptor activation process. Despite technical limitations in high-resolution structural determination of membrane proteins, the structures of several retinal proteins, including different intermediates of bR, halorhodopsin, rhodopsin, and sensory rhodopsin II, have been solved by X-ray crystallography.

In order to investigate the mechanism by which light energy is absorbed and stored in retinal proteins, the primary photo-induced step of activation in bR, namely retinal's photoisomerization, was simulated using a combined molecular mechanical and quantum mechanical approach, in which the chromophore's excited state dynamics was calculated at a high quantum mechanical level, while electrostatic interactions and coupling of motion of the chromophore and the protein were described using an empirical force field [82]. The results revealed that both bond-selectivity and unidirectionality of retinal's isomerization in bR are dictated by the protein through specific interactions, which effectively block any variation of the

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

†URL: `http://www.ks.uiuc.edu/Research/rhodopsin/`

isomerization reaction. The results illustrate the essential role of the protein for the characteristic kinetics and high selectivity of the photoisomerization; the protein impedes inhomogeneous photoisomerization paths and funnels them into a single path that initiates the functional process. Supported by comparison with dynamic spectral modulations observed in femtosecond spectroscopy, the results identify the principal molecular motion during photoisomerization [82].

The primary photo-induced conformational changes of the visual receptor rhodopsin was simulated by the Resource using a fully hydrated model of the protein in a membrane [83]. After equilibration of the structure, retinal isomerization and early activation steps were studied in a 10 ns molecular dynamics simulation. The isomerization completes within 150 fs and yields a strongly distorted retinal. The most significant conformational changes in the binding pocket are straightening of retinal's backbone and separation of its ring from Trp265. In the following 500 ps, transition of 6*s-cis* to 6*s-trans* retinal and dramatic changes in the hydrogen bonding network of the binding pocket involving the counterion for the protonated Schiff base, Glu113, occur. The energy initially stored internally in the distorted retinal is transformed into non-bonding interactions of retinal with its environment. During the following ten nanoseconds, increased mobilities of some parts of the protein, such as the kinked regions of the helices, mainly helix VI, and the second intracellular loop, were observed, as well as transient structural changes involving the conserved salt bridge between Glu134 and Arg135. These features prepare the protein for major structural transformations achieved later in the photocycle. Retinal's motion, in particular, can be compared to an opening turnstile freeing the way for the proposed rotation of helix VI [83].

BTA UNIT: C

TITLE: Light-harvesting in Photosystem I

KEYWORDS: bioenergetics, photosynthesis, excitation transfer

AXIS I: 7a, 8, 9

AXIS II: 77, 84

INVEST1: Melih K. Sener
DEGREE1: Ph. D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Sanghyun Park
DEGREE2: B. S.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: Deyu Lu
DEGREE3: B. S.
DEPT3: Beckman Institute
NONHOST3:

INVEST4: Thorsten Ritz
DEGREE4: Ph. D.
DEPT4: Department of Biology
NONHOST4: Virginia Polytechnic Institute and State University

INVEST5: Petra Fromme
DEGREE5: Ph. D.
DEPT5: Department of Chemistry and Biochemistry
NONHOST5: Arizona State University

% BTA $: 4 %

ABSTRACT: The respiratory chain of mammals and the photosynthetic apparatus of plants and bacteria share homologous enzymes. Therefore the study of the electrochemical processes in photosynthetic organisms provides insight for similar processes in eukaryotic mitochondria, where it is more difficult to attempt a direct study. In the past funding period the Resource continued its collaboration with P. Fromme from Arizona State University to study the excitation transfer mechanism in the protein-pigment complex photosystem I (PSI) of the cyanobacterium *Synechococcus elongatus* [84]*.

The earlier studies of the Resource, based on an effective Hamiltonian formulation of the chlorophyll aggregate in PSI, have quantitatively reproduced the observed quantum yield and average excitation lifetime of the system [85]. Furthermore, the chlorophyll network of PSI has been revealed to be highly robust against pruning of individual chlorophylls. The chlorophyll network, which contains 96 chlorophylls, has no apparent symmetries, in contrast to the highly symmetrical chlorophyll arrangement in purple bacteria [86]. In an effort to provide a simplifying picture for the complex chlorophyll network of PSI, a reaction path method based on mean first passage times was developed, revealing representative pathways along which excitation migrates from the periphery of the chlorophyll network towards the reaction center [87]. This approach incorporates information about all possible reaction events as well as the effect of temperature. The paths thus computed provide a complete, yet distilled, representation of the kinetic flow of excitation towards the reaction center, thereby succinctly characterizing the function of the system.

PSI in cyanobacteria is expressed either as a monomer or a trimer depending on external conditions such as light intensity and ion concentrations. An extension of the sojourn expansion, a method for studying excitation transfer processes in terms of repeated returns to a reaction center, has been formulated for an arbitrary number of reaction centers and applied to the trimeric form of PSI.

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

BTA UNIT: C

TITLE: Carbon Nanotubes as Models for Biological Channels

KEYWORDS: carbon nanotube, water permeation, proton conduction

AXIS I: 3

AXIS II: 39

INVEST1: Fangqiang Zhu
DEGREE1: M.S.
DEPT1: Physics
NONHOST1:

INVEST2: Deyu Lu
DEGREE2: M.S.
DEPT2: Physics
NONHOST2:

INVEST3: Umberto Ravaioli
DEGREE3: Ph.D.
DEPT3: Beckman Institute
NONHOST3:

INVEST4: Aluru Narayana
DEGREE4: Ph.D.
DEPT4: Beckman Institute
NONHOST4:

% BTA $: 2 %

ABSTRACT: Biological channels are usually complex, and the investigation of these channels is accordingly complicated. Carbon nanotubes can serve as prototypes for biological channels, that can be studied more easily by MD simulations [88] due to their simplicity and stability.

We modeled a (pristine) carbon nanotube with all atoms having zero charge, and then built several other types of nanotubes by assigning charges to a few atoms of the pristine nanotube. We performed MD simulations on both the pristine and the modified nanotubes. Water molecules inside the nanotubes exhibit a strong ordering of their dipole moments. In particular, bipolar water orientation was observed in a modified nanotube, as also found in aquaporin channels [18]. However,

water diffusion in the modified (polar) nanotubes becomes slower compared with that in the pristine (nonpolar) nanotube. We also applied the theory of network thermodynamics [89–91] to investigate proton conduction through the nanotubes [92].

BTA UNIT: C

TITLE: Membrane Scaffold Proteins

KEYWORDS: apolipoprotein A-I, self-assembly, protein engineering, nanotechnology, membrane protein solubilization

AXIS I: 3

AXIS II: 39, 89

INVEST1: James Phillips
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Stephen Sligar (and colleagues)
DEGREE2: Ph.D.
DEPT2: Department of Biochemistry
NONHOST2:

% BTA $: 2 %

ABSTRACT: Membrane proteins carry out metabolic reactions, ATP synthesis, and a variety of sensory and regulatory processes. High density lipoprotein (HDL) particles, in their nascent cholesterol-free state, comprise a small bilayer disk solubilized by the amphipathic helices of apolipoprotein A-I (apo A-I), which bind to and cover the exposed hydrophobic lipid tails and the edge of the disk. These HDL disks are the smallest functional bilayer found in nature, and may therefore provide a means of solvating isolated membrane proteins in their active, native state.

Bayburt, Grinkova, and Sligar have developed a process for manufacturing soluble lipoprotein disks [93]. They have termed the class of proteins used to solubilize the lipid bilayer *membrane scaffold proteins* (MSP). The sequence of MSP is based on that of human apo A-I with the initial 43-residue globular domain removed, leaving only the 200-residue lipid-binding domain. Based on existing models of HDL [94–97] and the known sequence and properties of MSP, we have constructed three models of MSP disks, each comprising over 144,000 atoms and simulated for 4.2 ns using NAMD [10]. Based on these models, we have suggested stabilizing mutations that have been experimentally confirmed to decrease the susceptibility of MSP disks to thermal degradation. Further experiments and simulations to confirm the structure of MSP disks and test alternate mutations are planned.

BTA UNIT: C, T

TITLE: Conformational Changes in a Holliday Junction

KEYWORDS: DNA structure, recombination,Holliday junction, free energy

AXIS I: 2

AXIS II: 74g, 89

INVEST1: Fatemeh Khalili-Araghi
DEGREE1: B.S.
DEPT1: Physics
NONHOST1:

INVEST2: Jin Yu
DEGREE2: M.S.
DEPT2: Physics
NONHOST2:

INVEST3: Taekjip Ha
DEGREE3: Ph.D.
DEPT3: Physics
NONHOST3:

% BTA $: 2 %

ABSTRACT: Homologous genetic recombination is a fundamental process of all cells. It is important in the repair of breaks in double stranded DNA, and provides a means of generating genetic diversity [98]. The 4-way junction is the central intermediate of this process. In solution, there is an equilibrium between two alternative stacked forms. Crystal structures of Holliday junctions have been determined in a single stacking conformer [99–101], which implies a strong bias toward one conformer [102]. Transition between alternative conformers has been detected experimentally, using FRET or NMR methods [103]. During this transition, the junction passes through an open structure [102].

Using the available crystal structure [99] as well as mutated forms generated with VMD [47], the Resource has studied the relative stability of different conformers, their sequence dependence and the influence of counter-ions on the transition. The system was simulated using the molecular dynamics program NAMD [104] and contained 40,000 atoms. Further studies will employ steered molecular dynamics to explore the pathway of the transition to open state.

In order to investigate the global aspects of the conformational transition between the stacked and the open states, as well as between the open state and the alternative stacked state, a simplified model using two or three degrees of freedom is employed. Rather than performing a single long simulation, the dynamics of this simplified model can be studied through a series of short simulations on multiple intermediate states. Using information about the local energy profile obtained for these states, an iterative algorithm for escaping local energy minima [105] is applied to construct the free energy surface, which also reveals the possible dynamics of global conformational changes in the Holliday junction.

BTA UNIT: C

TITLE: Protein Stability at Negative Pressure

KEYWORDS: Protein folding, ubiquitin, pressure, density

AXIS I: 2,9

AXIS II: 74h

INVEST1: Martin Gruebele
DEGREE1: Ph.D., Professor
DEPT1: Chemistry, Physics, and Biophysics and Computational Biology
NONHOST1:

INVEST2: Edgar Larios
DEGREE2: M.S.
DEPT2: Physics
NONHOST2:

% BTA $: 1 %

ABSTRACT: ABSTRACT

Understanding how a protein acquires its unique 3-D structure is one of the most challenging scientific questions today. A simple chain of, say, 100 amino acids, has at least 2^{100} conformations that can not be totally sampled within the observed folding time scale. Moreover, it is not well understood how proteins interact with the solvent. This second problem is addressed in the present study exploring the use of solution densities that are lower than that of water under atmospheric pressure.

Molecular Dynamics (MD) has been successfully applied to study water under exotic conditions such as negative pressure. New states on the phase diagram of water have been found by groundbreaking computational work in the last decade [106, 107]. However, there has not been an experimental necessity to simulate biological systems under negative pressure. The Gruebele group at the University of Illinois has succeeded in studying the stability of the protein ubiquitin at densities lower than 1 g/cm^3. Their results clearly show that for pressures of about -100 atm, ubiquitin becomes more unstable.

The Resource has carried out MD on ubiquitin at negative pressure using NAMD [10]. The NPT ensemble was used to mimic experimental conditions. Visualization and analysis of simulation trajectories were performed using VMD [47]. The size of the system simulated was about 20,000 atoms. A total of 10 ns of trajectories were

obtained on the Resource's clusters. The results show that ubiquitin is indeed more unstable at pressures ranging between 0 and -1500 atm. Additionally, the results show a trend that for even lower pressures, the protein might become more stable, hence agreeing with protein experiments in vacuum [108].

BTA UNIT: C

TITLE: Ammonia Conduction through HisF

KEYWORDS: Ammonia, $\alpha\beta$-barrel proteins, histidine biosynthesis, glutamine amidotransferase, gating mechanism

AXIS I: 2

AXIS II: 74c, 89

INVEST1: Zaida Luthey-Schulten
DEGREE1: Ph.D.
DEPT1: Chemistry
NONHOST1:

INVEST2: Emad Tajkhorshid
DEGREE2: Ph.D.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: Rommie Amaro
DEGREE3: M.S.
DEPT3: Chemistry
NONHOST3:

% BTA $: 1 %

ABSTRACT: Amino acid biosynthesis is an ancient and fundamental process, and the metabolic pathways involved are represented in a diversity of organisms spanning the three domains of life. HisH-HisF is a multidomain enzymatic complex that catalyzes the 5th step of histidine biosynthesis. The two enzymes are found as separate polypeptide chains in bacteria, whereas in some higher organisms they are expressed as a single protein, which increases the probability of complex formation. HisH is a class I glutamine amidotransferase that hydrolyzes glutamine to form ammonia, a substrate which is then incorporated in the ring of a histidine precursor by HisF, a $\alpha\beta_8$ barrel cyclase. The active site of HisF, where ammonia is used is about 25 Å away from the catalytic site of HisH, where ammonia is generated. It is therefore postulated that the inner cavity of the barrel of HisF is used for conduction of the ammonia from the first active site to the second one. This type of substrate channeling is an uncommon function for an $\alpha\beta_8$ barrel fold. The channel entrance

is controlled by four charged residues that form a salt bridge gate. In the crystal structure [109] the gate has been captured in a closed conformation.

In collaboration with the group of Luthey-Schulten, Department of Chemistry, UIUC, the Resource has conducted a series of molecular dynamic simulations in which the channeling function of HisF was investigated [110]. The simulations included a model of HisF-HisH complex solvated in water, which resulted in a system of more than 50,000 atoms. Several conformations of gate-forming residues were examined by interactive molecular dynamics [23]. This resulted in a low-energy, open-gate configuration in which charged residues of the gate form stabilizing hydrogen bonds with nearby side chains of both HisF and HisH. Conduction of ammonia through the channel was simulated using steered molecular dynamics [60, 111], in which an ammonia molecule was pulled through the channel in either direction. In order to improve the statistics, the simulations were repeated eight times for both the closed-gate (crystal structure) and open-gate (modeled) configurations, each lasting 1.2 ns. From these pulling experiments, free energy profiles of conduction of ammonia through open and closed channels were calculated, and the interaction of ammonia with the channel was analyzed.

The results [110] clearly indicate a high barrier against the conduction of ammonia in the crystal structure of the complex, suggesting that conformational changes of residues in the gate region are required for channeling function. In the open configuration, one of the gate residues in HisF is interacting with side chains of HisH. Therefore, it can be proposed that the formation of the HisF-HisH complex facilitates the opening of the channel, which must be kept closed when no substrate is present. Such a gating mechanism may prevent the hydration of the channel interior of HisF, and therefore decrease the chance of formation of a protonated ammonia, which is chemically inactive. Though the channel is predominantly hydrophobic, it is evident from the analysis that the conserved hydrophilic residues within the channel are essential to the conduction of ammonia. Mutations of the interacting residues should affect the free energy profile of ammonia in the channel, as well as the overall reaction kinetics.

BTA UNIT: T,S

TITLE: Fast Methods for Electrostatics and Polarization

KEYWORDS: fast electrostatic methods, hierarchical interpolation,polarization

AXIS I: 9

AXIS II: 42

INVEST1: David J. Hardy
DEGREE1: M.S.
DEPT1: Department of Computer Science
NONHOST1:

INVEST2: Wei Wang
DEGREE2: M.S.
DEPT2: Department of Computer Science
NONHOST2:

INVEST3: Robert Skeel
DEGREE3: Ph.D.
DEPT3: Beckman Institute
NONHOST3:

% BTA $: 3 %

ABSTRACT: NAMD [10] uses the fast multipole algorithm implemented in DPMTA [112] for the calculation of electrostatic forces for nonperiodic systems and particle-mesh Ewald (PME) [113] for periodic systems. The performance of the multipole algorithm is a bottleneck for performance, and in recent years an alternative approach based on a hierarchical interpolation of softened pairwise potentials on multiple grids has been explored [114, 115]. Recent 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. In the past year the method has been implemented for Ewald periodic boundary conditions and demonstrated to be competitive with PME. A periodic multiple grid algorithm is more scalable than PME and is part of a more general approach to the treatment of nonbonded forces. Work is being done to improve efficiency and obtain further evidence of reliability of the multiple grid method.

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

A consensus has emerged among researchers favoring the inclusion of electronic polarizability in simulations [116], but problems remain concerning the robustness and high computational cost of proposed models and algorithms. As a result, few simulations actually incorporate the effects of induced polarization. The goal of the second part of this subproject is to identify superior models and to construct much faster algorithms so that polarizability becomes a routine part of MD simulations. The point dipole model is chosen because it is implemented in the latest version of AMBER [117], and a self-consistent implementation is chosen because it is applicable to kinetic as well as thermodynamic calculations and because it is a standard against which other approximation approaches can be compared. Software is being written and tested for a sequential molecular dynamics program and is intended to be incorporated into the next major release of NAMD [10]. Using standard numerical techniques, the performance of the polarization calculation has already been doubled over that reported in the literature [118].

BTA UNIT: D,S

TITLE: Training

KEYWORDS: training, learning, education

AXIS I: 28

AXIS II: 51

INVEST1: Michael Bach
DEGREE1: B. S.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Gila Budescu
DEGREE2: Ph. D.
DEPT2: Beckman Institute
NONHOST2:

% BTA $: 4 %

ABSTRACT: The Resource recognizes the vital importance of training for the education and professional growth of young scientists. We have begun in the past 12 months to expand web-based training venues and we have created a new training section on our site*. This section includes tutorials using Resource tools, links to relevant classes and to other online teaching tools useful in developing teaching contents and techniques within the Resource. The training section is regularly updated as the Resource explores new strategies for online training.

The Resource has given demonstrations of NAMD, VMD, and BioCoRE, and is engaged in developing science tutorials.

A major development has been the new BioCoRE capability to create public project areas (see p. 31). While until recently BioCoRE was organized around private projects only visible to members of those projects, now any BioCoRE user may join a public project, making it easy for researchers to disseminate training materials within BioCoRE. This further facilitates broader interactions and discourse between experienced and novice researchers. On the main BioCoRE server, for example, we have added a public "BioCoRE Help" project to help new users with any problems they may have.

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

Future training plans include links to the Resource's 2003 Summer School (see Training p. 112), an updated tour for BioCoRE, a Tutorial tool within BioCoRE, and continuous demos and tutorials.

BTA UNIT: S

TITLE: Computational Facility

KEYWORDS: parallel computing, visualization, network

AXIS I: 11

AXIS II: 42,89

INVEST1: Tim Skirvin

DEGREE1: B.S.

DEPT1: Theoretical and Computational Biophysics

NONHOST1:

% BTA $: 7%

ABSTRACT: In the past year the Resource has improved its current computational facility* in four main categories: local Linux cluster, Linux-based desktop workstations, public visualization, and data storage and backup infrastructure. The changes have allowed us to cost-effectively expand our ability to analyze ever-larger molecular systems and to better maintain our local resources. The Resource currently has 49 local users, and 86 overall.

In May 2003 the Resource plans to purchase an additional 96-processor Linux cluster, with installation to be complete by the end of June. With the 64 nodes of our current facility, this more than doubles the local computational power of last year. The new nodes will be managed through the open-source ClusterMatic package, which will allow for maximum flexibility while maintaining our current level of utilization and manageability.

The last year has seen a large push towards Linux-based workstations as desktops. The Resource currently has 24 Linux systems on researcher desktops, which previously were nodes of our computational cluster; we plan to increase these to 36 by July. Additionally, we are in the process of upgrading the administrative Apple systems to newer systems, to better manage our resources.

Our research continues to push the limits of our shared visualization systems. We currently maintain eight shared stereo-capable workstations, and have already ordered six more such workstations. These systems, which are primarily Suns, are capable of analyzing larger systems and viewing them in stereo.

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

We also plan to upgrade our server environment shortly. We have ordered four SunFire 280R servers to supplement and replace our existing file and application servers. With this upgrade the Resource will nearly double its shared disk space to a total of 4.5TB of data. This data is backed up nightly using SuperDLT tape drives and in-house software. Additional services are managed using Sun Netra X1 and V100 servers.

Our supercomputer time over the last year has been consolidated onto primarily one system (PSC's LeMieux) for maximum utilization. We also maintain accounts and time on NCSA's Titan Linux and p390 Regatta clusters.

Resource Summary

Resource Summary (2002–2003)

	T	C	D	S	T-C-D	TOT
Number of Publications	13	5		6*	6	30
Number of Subprojects	12	13	3	7		**
Number of Investigators	43	46	15	21		***
Percent of BTA funds Allocated	40%	35%	12.5%	12.5%		100%
Service Fees Collected	0	0	0	0	0	0
Other Funds ($)	$200,000	$100,000	$30,000			$330,000

T: Technological research and development

C: Collaborative research

S: Service

D: Dissemination and training

T-C-D: represents overlapping areas

*Software releases.

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

***Total number of investigators is 64, and is not the sum of T, C, D, and S contributors as counted above.

Geographical Data (2002–2003)

State or Country	Number of Investigators
IL	50
WA	1
CA	1
CO	1
WI	1
TX	1
VA	1
AZ	1
Germany	2
Israel	1
Japan	1
Italy	1
UK	1
Denmark	1

BTA Unit T (2002–2003)

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Aksimentiev, Aleksei		FED	NSF
Bach, Michael		FED	NIH
Balabin, Ilya		FED	NIH NSF
Balaeff, Alexander		FED OTH	NIH
Brandon, David		FED	NIH
Braun, Rosemary		FED	NSF
Brunner, Robert		FED	NIH
Budescu, Gila		FED	NIH
Caddigan, Eamon		FED	NIH
Cohen, Jordi		FED	NSF
Dagit, Derek		FED	NIH
DeSouza, Jayant		FED	NIH
Dittrich, Markus		FED	NSF
Fillingame, Robert	University of Wisconsin, Madison (Fillingame)	OTH	
Grayson, Paul		OTH	

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Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Gullingsrud, Justin		FED	NIH
Ha, Taekjip	University of Illinois (Ha)	OTH	
Hardy, David		OTH	
Hayashi, Shigehiko		FED OTH	NIH
Isralewitz, Barry		FED	NIH NSF
Kale, Laxmikant		FED	NIH
Kanchanawarin, C.		OTH	
Kandori, Hideko	Kyoto University, Japan (Kandori)	OTH	
Khalili-Araghi, F.		OTH	
Kumar, Sameer		FED	NIH
Landau, Ehud M.		OTH	
Mahadevan, L.	University of Cambridge (Mahadevan)	OTH	
Olivucci, Massimo	Univeersity of Sienna, Siena, Italy (Olivucci)	OTH	
Park, Sanghyun		FED	NSF
Phillips, James		FED	NIH
Potnuru, Mani		FED	NIH
Saam, Jan		OTH	

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Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	**AGENCY**
Sheves, Mordechai	Weizmann Institute, Rehovot, Israel (Sheves)	OTH	
Skeel, Robert		FED	NIH
Sotomayor, Marcos		FED	NIH
Stone, John		FED	NIH
Suhai, Sandor	German Cancer Res. Inst., Heidelberg (Suhai)	OTH	
Tajkhorshid, Emadeddin		FED OTH	NIH NSF
Vandivort, Kirby		FED	NIH
Villa, Elizabeth		FED	NSF
Wang, Wei		OTH	
Yu, Jin		OTH	
Zheng, Gengbin		OTH	

BTA Unit C (2002–2003)

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Aksimentiev, Aleksei		FED	NSF
Amaro, Rommie	University of Illinois (Luthey-Schulten)	OTH	
Balabin, Ilya		FED	NIH NSF
Balaef, Alexander		FED OTH	NIH
Bayas, Marco V.		OTH	
Braun, Rosemary		FED	NSF
Dittrich, Markus		FED	NSF
Engelman, Donald M.		OTH	
Fillingame, Robert	University of Wisconsin, Madison (Fillingame)	OTH	
Fromme, Petra	Arizona State University (Fromme)	OTH	
Gao, Mu		OTH	
Grayson, Paul		OTH	
Gruebele, Martin	University of Illinois (Gruebele)	OTH	
Gullingsrud, Justin		FED OTH	NIH
Ha, Taekjip	University of Illinois (Ha)	OTH	

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Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	**AGENCY**
Hayashi, Shigehiko		OTH FED	 NIH
Isralewitz, Barry		FED	NIH NSF
Jensen, Morten	Technical University of Denmark	OTH	
Kandori, Hideko	Kyoto University, Japan (Kandori)	OTH	
Kanchanawarin, C.		OTH	
Khalili-Araghi, F.		OTH	
Landau, Ehud M.	University of Texas Medical Branch (Landau)	OTH	
Larios, Edgar	University of Illinois (Gruebele)	OTH	
Leckband, Deborah	University of Illinois (Leckband)	FED	NIH
Lu, Deyu		OTH	
Lu, Hui	University of Illinois - Chicago (Lu)	OTH	
Luthey-Schulten, Zaida	University of Illinois (Luthey-Schulten)	OTH	
Mahadevan, L.	University of Cambridge (Mahadevan)	OTH	
Narayana, Aluru		OTH	
Olivucci, Massimo	Univeersity of Sienna, Siena, Italy (Olivucci)	OTH	
Park, Sanghyun		FED	NSF
Phillips, James		FED	NIH
Ravaioli, Umberto		OTH	

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Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	**AGENCY**
Ritz, Thorsten	Virginia Polytech Institute (Ritz)	OTH	
Saam, Jan	Humboldt University, Berlin, Germany	OTH	
Sener, Melih		FED	NIH
Sheves, Mordechai	Weizmann Institute, Rehovot, Israel (Sheves)	OTH	
Sligar, Stephen	University of Illinois (Sligar)	OTH	
Stroud, Robert	University of California, San Francisco (Stroud)	OTH	
Suhai, Sandor	German Cancer Res. Inst., Heidelberg (Suhai)	OTH	
Tajkhorshid, Emadeddin		FED OTH	NIH NSF
Villa, Elizabeth		FED	NSF
Vogel, Viola	University of Washington (Vogel)	OTH	
Willmans, Matthias	EMBL Hamburg Outstation (Willmans)	OTH	
Yu, Jin		OTH	
Zhu, Fangqiang		OTH	

BTA Unit D and S (2002–2003)

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Bach, Michael		FED	NIH
Brandon, David		FED	NIH
Braun, Rosemary		FED	NSF
Brunner, Robert		FED	NIH
Budescu, Gila		FED	NIH
Caddigan, Eamon		FED	NIH
Dagit, Derek		FED	NIH
DeSouza, Jayant		FED	NIH
Gullingsrud, Justin		FED OTH	NIH
Hardy, David		OTH	
Kale, Laxmikant		FED	NIH
Kumar, Sameer		FED	NIH
Phillips, James		FED	NIH
Potnuru, Mani		FED	NIH
Skeel, Robert		FED	NIH

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Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Skirvin, Tim		FED	NIH
Stone, John		FED	NIH
Vandivort, Kirby		FED	NIH
Villa, Elizabeth		FED	NSF
Wang, Wei		OTH	
Zheng, Gengbin		OTH	

Advisory Committee

The Resource advisory board met last time on May 2, 2001, just before the Resource submitted its 5-year renewal application. In the spring of 2002 the Resource had the site visit associated with the review process and renewed funding had started on August 1, 2002.

In the past several months we have tried to schedule the first advisory board meeting of the new funding cycle. Due to the very busy schedule of our esteemed board members, a meeting scheduled for May, 2003 had to be postponed and has already been rescheduled for September 18, 2003.

The members of the Advisory Board are:

- Angela Gronenborn, NIH
- Benoit Roux, Cornell
- Mary Schuler, UIUC
- Jeff Skolnick, Buffalo
- Marc Snir, UIUC

The board will review our performance since Aug. 1, 2002 and will offer suggestions and comments on our planned research and development efforts. Since the upcoming meeting of the advisory board will be the very first one following our successful renewal, it will be of critical importance in shaping our directions for the coming year/s.

Organization

Organizational Structure

In the past year we have continued to create and transfer new administrative services from proprietary interfaces to the web. 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. Our seminars are now maintained in a newly-developed database* and soon all talks offered by Resource members will be stored in a similar fashion.

Just like our approach toward cluster computing, we are committed to cost-effective solutions in all other areas in order to sustain effective administration. The Resource's web site represents our way of seeing and doing things both within and beyond the Resource's formal boundaries. Recent additions to our external website include a new poster gallery†, and a revamped VMD gallery will be soon available, as well as a developer tool page which will inform visitors and users of the extensive tools used in our development activities.

The Resource's organizational structure is determined by its mission and nature of activities. It is shown in Fig. 5.

K. Schulten (Professor, Physics, Beckman, Biophysics, Chemistry) is the Principal Investigator and Program Director of the Resource. G. Budescu (Managing Director and Research Scientist), L. Kalé (Professor, Computer Science) and R. Skeel (Professor, Computer Science) are Co-Principal Investigators, and the Assistant Director for Research is Emad Tajkhorshid. 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 (see p. 80).

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. The graduate assistants are affiliated with departments such as Physics, Computer Science, Biophysics, Chemistry, Speech Communication, 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

*URL: `http://www.ks.uiuc.edu/Services/Seminar/`

†URL: `http://www.ks.uiuc.edu/Overview/gallery/posters/`

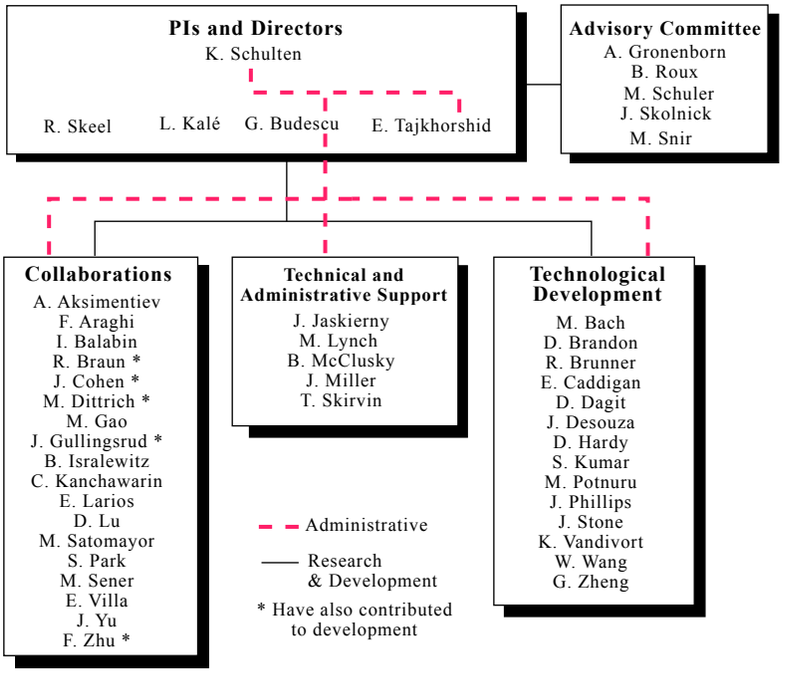

Figure 5: Resource Organizational Structure

by spending time at the Beckman Institute as well as through email and the Resource's internal web site which lists meetings, seminars, group jobs, and more.

Collaborative and service projects are determined by the PIs and affiliated faculty, in consultation with the other Resource members. 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 projects

Continuous interactions with the 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 old 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 leads users and beneficiaries to guidelines on how to acknowledge Resource support in several ways[‡], depending on the resources used.

[‡]Acknowledgement guidelines are at `http://www.ks.uiuc.edu/Overview/acknowledge.html`

Service, Training and Dissemination

Service, Training and Dissemination

Our service, training, and dissemination are boundary spanning activities through which we transfer the outcomes of our work and deliver technologies and knowledge to the 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. Our service, training, and dissemination are boundary spanning mechanisms through which we transfer the outcomes of our work and deliver technologies and knowledge to the community.

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 size of the Resource is un-precedented— over 40 members (graduate assistants, postdoctoral associates, developers, faculty, administrative and technical staff); the number and size of systems modeled here are unmatched; our computational resources are much bigger 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. Consequently, organizational boundaries are becoming blurrier and more flexible than ever before, thereby impacting our strategic thinking and daily operation. Immense opportunities for better administration, service, training and dissemination are available now and with them related issues such as intellectual property, ownership, copyright matters, licensing, and more have to be considered and addressed.

While in the past our focus was mostly on web-based dissemination and services, in the last year we have begun to substantially expand and develop our web-based training capabilities. The growing functionality of BioCoRE and of high bandwidth communication networks makes the Resource especially well positioned to achieve this expansion.

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 collaborations, as evidenced by the collaborative projects outlined earlier.

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.

86 researchers have used the Resource's computational facilities (49 local, 37 remote). By June 2003 the Resource will have an increase of 63% in shared file storage space compared to the same period a year ago (from 2785 to 4530 GB). In that same period, the Resource increased its local computer power by 20% and external supercomputer time has again been allocated. The Resource's local visualization capacity has grown in the past year by 10%.

Our knowledge of visualization solutions, large-memory computers, web utilization, and computational clusters has been of specific use to the biomedical community; many researchers have requested and received our advice for their local facilities. These include (in chronological order starting in June 2002):

- Chemistry @ UIUC (system configuration)
- Bioengineering @ UIC (cluster building)
- NCSA & CAVE (VMD updates)
- Jan Saam (cluster related matters)
- Beckman ITG (networking issues)
- Mol. Biology @ Princeton (3d viz systems)
- Wabash College (cluster building)
- University of Missouri - Columbia (cluster building)
- BASF (cluster building)
- Johns Hopkins University (cluster building)
- Harvard (cluster building)
- Tulane (platform selection for MD)
- University of Alabama, Birmingham (cluster building)

- UCSF (cluster building)
- Chemistry @ UIUC (cluster building)
- University of Technology, Sydney (compiler information)
- Queen's University (cluster building)
- Johns Hopkins (platform selection for MD)
- Woodrow Wilson High School, New Jersey (cluster building)
- Los Alamos National Laboratory (parallelization issues)
- University of Missouri - Columbia (cluster building)
- Johns Hopkins, (cluster building)
- UIUC CITES WSG (cluster building)
- Beckman BISS (advice on BI website development— organization, format, and technical aspects)

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, HP, IBM. Among other benefits to our users, such cutting edge testing increases the likelihood of easy porting of our software once the new 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.*

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

Our software distribution process consists of three web-based steps: registration, licensing, and download. The first step, registration, is mandatory for our larger programs (NAMD, VMD, BioCoRE), and consists of providing minimal, yet necessary, personal information in order to let us track usage patterns of our software. Later downloads can skip this registration through the use of a login and password. The second step, licensing, consists of agreeing to the software's license agreement; this essentially states:

- The software belongs to the University of Illinois and the Resource;
- The user may use the software freely, but may not redistribute it;
- If used for research, the Resource's contribution must be cited.

Finally, once the license is agreed to (by clicking "I agree"), the software download begins. The users may then install or access the software at their leisure. All registration information and download data are stored in a local database, and can be easily mined for periodical user surveys, ongoing statistics and user contact information. Some packages require more and some less effort to develop and maintain. They have all been contributed and maintained by Resource developers and researchers. Once the packages are on our web site they are treated with the same professional criteria of quality, support, and care as NAMD, VMD and BioCoRE.

In this report we are focusing on the distribution and support accomplishments of NAMD, VMD and BioCoRE, in the past year.

Use of VMD, NAMD, and BioCoRE The VMD, NAMD and BioCoRE programs are developed, maintained, and distributed by Resource staff. The staff also offers extensive 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 29,058 of which 6,641 are repeat users. The latest version, VMD 1.8, boasts 6,631 users, of whom 1,296 are NIH funded. VMD had been downloaded 29,391 in the past year.

NAMD has 5,989 registered users, of whom 1,102 are repeat users. 920 of NAMD users are NIH funded. NAMD had been downloaded 6,756 times in the past year.

BioCoRE has currently 592 registered users (an increase of 181 in the past year), involved in 158 projects (compared to 95 a year ago). 72 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 on 12/10/2002; 1.8.1 in May 2003.
- NAMD: 2.5b1 on April 18, 2002; 2.5b2 and 2.5 in May 2003; overall redesign and initial release of NAMD3 by December, 2003.
- BioCoRE: Incremental updates every few weeks.† Key features were released as follows: Java Molecular Viewer (JMV) support within BioCoRE in July 2002; Server source code release on Dec. 9, 2002; WebDAV support in May 2003.

We are maintaining ongoing discussions with industry regarding collaborative projects and special licenses for our software. More often than not outcomes depend on the UIUC Tecnology Management Office.

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 web hits.)

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

	Total	Month Avg.
VMD	109,200	11,554
NAMD	43,066	4,669
BioCoRE	20,015	2,001

All three sections show a significant increase compared to the monthly averages the year before (VMD +40%; NAMD +44%; BioCoRE +250%)

VMD, NAMD and BioCoRE Key Accomplishments in Past 12 Months

VMD 2002–03 VMD updates include:

- Completely rewritten graphical user interface adopting standard interface design paradigms for improved ease-of-use
- Native support for MacOS X windowing system and OpenGL
- New AMBER 7, XYZ, X-PLOR electron density map, and Gaussian "cube" file reader plugins

†Complete schedule at `http://www.ks.uiuc.edu/Research/biocore/announce/changeLog.shtml`

- Support for OpenGL rendering features and extensions which provide enhanced performance and visual quality
- Movie making capabilities with support for real-time screen capture, built-in ray tracing, and external renderers
- Dynamic recalculation of bonds for improved display of ab initio simulations
- Significant performance improvements in display, script execution, external rendering
- Improved support for CAVE environments using CAVElib and FreeVr, and tiled display walls using WireGL and Chromium
- Improved BioCoRE-based collaboration features allowing molecule coordinate files stored in BioFS to be used in molecular graphics sessions
- Display of periodic images for MD trajectories of periodic systems or for any molecule with translational periodicity

VMD demonstrations offered in the past year (local and remote, by Resource members and others who informed us)

- VMD/JMV demonstrations at Siggraph 2002 (J.Stone and M. Bach)
- VMD demonstrations at SC2002 (Sun Microsystems, J. Phillips)
- VMD movie played during NSF Director's keynote at SC2002
- VMD 3-D demo logs 4/15/2002–4/15/2003:
  - 144 VMD demos in the NCSA CAVE
  - 59 VMD demos in the Resource facility

126 individuals outside of the Resource currently have access to the VMD source code.

Scope of VMD User Support:

- 930 unique correspondents sent us VMD support requests in 2002-2003
- 6506 emails issued to/from vmd@ks.uiuc.edu for in 2002–03
- Local face-to-face support has been provided.

List of papers citing VMD: A literature search in April 2003 through ISI Web of Knowledge yielded 142 published papers that cited the use of VMD over the past year:

1. Hetenyi, C., Szabo, Z., Klement, T., Datki, Z., Kortvelyesi, T., Zarandi, M., Penke, B., "Pentapeptide amides interfere with the aggregation of beta- amyloid peptide of Alzheimer's disease," Biochem. Biophys. Res. Commun. 292, 931-936 (2002).

2. Tuma, J., Connors, W.H., Stitelman, D.H., Richert, C., "On the effect of covalently appended quinolones on termini of DNA duplexes," J. Am. Chem. Soc. 124, 4236-4246 (2002).

3. Pomes, R., Roux, B., "Molecular mechanism of H+ conduction in the single-file water chain of the gramicidin channel," Biophys. J. 82, 2304-2316 (2002).

4. Humbird, D., Graves, D.B., "Ion-induced damage and annealing of silicon. Molecular dynamics simulations," Pure Appl. Chem. 74, 419-422 (2002).

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11. Zubrzycki, I.Z., "Homology modeling and molecular dynamics study of NAD-dependent glycerol-3-phosphate dehydrogenase from Trypanosoma brucei rhodesiense, a potential target enzyme for anti-sleeping sickness drug development," Biophys. J. 82, 2906-2915 (2002).

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13. Jensen, M.O., Park, S., Tajkhorshid, E., Schulten, K., "Energetics of glycerol conduction through aquaglyceroporin GlpF," Proc. Natl. Acad. Sci. U. S. A. 99, 6731-6736 (2002).

14. Wong, F.C., Beuning, P.J., Nagan, M., Shiba, K., Musier-Forsyth, K., "Functional role of the prokaryotic proline-tRNA synthetase insertion domain in amino acid editing," Biochemistry 41, 7108-7115 (2002).

15. Ming, D.M., Kong, Y.F., Wakil, S.J., Brink, J., Ma, J.P., "Domain movements in human fatty acid synthase by quantized elastic deformational model," Proc. Natl. Acad. Sci. U. S. A. 99, 7895-7899 (2002).

16. Kozlenkov, A., Manes, T., Hoylaerts, M.F., Millan, J.L., "Function assignment to conserved residues in mammalian alkaline phosphatases," J. Biol. Chem. 277, 22992-22999 (2002).

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21. Zhu, F.Q., Tajkhorshid, E., Schulten, K., "Pressure-induced water transport in membrane channels studied by molecular dynamics," Biophys. J. 83, 154-160 (2002).

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9. Morrow, T.I., Maginn, E.J., "Molecular dynamics study of the ionic liquid 1-n-butyl-3-methylimidazolium hexafluorophosphate," J. Phys. Chem. B 106, 12807-12813 (2002).

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12. Gao, M., Wilmanns, M., Schulten, K., "Steered molecular dynamics studies of titin I1 domain unfolding," Biophys. J. 83, 3435-3445 (2002).

13. Saam, J., Tajkhorshid, E., Hayashi, S., Schulten, K., "Molecular dynamics investigation of primary photoinduced events in the activation of rhodopsin," Biophys. J. 83,

3097-3112 (2002).

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Major Sites with Links to NAMD Site (Google, Apr. 2003): There are over 140 domains, sites, and pages with links to the NAMD site.

BioCoRE 2002–03 BioCoRE updates include:

- WebDAV support - this new support for the BioFS allows popular operating systems (Windows XP, Mac OS X, Linux) to access the BioFS as if it is a network drive. Native applications can read and write files directly to and from the BioFS.
- BioCoRE@NCSA— BioCoRE team and NCSA established a new BioCoRE server[‡], giving NCSA users easier access to BioCoRE.
- Public/Private Domains— Users can now set up public areas for their project, allowing any BioCoRE users (not just researchers in their own project) to see message board messages, web site links, or participate in chats, while still keeping public data separate from private data.

[‡] `http://biocore.ncsa.uiuc.edu`

- Remote File Uploading— Job Management now allows input files to be uploaded from the BioFS to the remote supercomputer account to serve as input data for a supercomputer job, and also allows a list of output files to be retrieved to the BioFS upon completion of the job.

- Shared Notes— A Lab Book is now available for researchers to record notes and updates about their project. Other project members can review the notes and find out what each person is doing.

- JMV— A Java-based molecular viewer allows users to view and manipulate pictures of molecules without having an external application such as VMD installed.

- Updated BioCoRE Face— A new BioCoRE web page appearance gives improved usability and better compatibility with various web browsers.

BioCoRE Evaluation The BioCoRE ever-present evaluation component is another facet of our commitment to quality service. By being consistently tuned in to our users' preferences, attitudes and experiences we are well informed on how to respond and meet their needs. The activities of the BioCoRE evaluation team over the last year fall roughly into three categories: conceptual development, data collection, and prototype creation. To provide a context for evaluation data, a multi-theoretical report applying several technology assessment theories (e.g. Diffusion of Innovations, the Technology Acceptance Model) to BioCoRE was produced following reviews of the utility of each model with the development team. Several measures utilizing unobtrusive data collected by BioCoRE were developed to describe user behavior (individually, within projects, and across BioCoRE) and tool access in terms of gross use, gross use over time, distribution of use, and distribution of use over time. More data collection was accomplished via the BioCoRE 2002 user survey, in which registered users were asked to complete a web-based survey collecting basic user data, responses to questions based on usability concepts, and reactions to open questions. In response to prior evaluation data, the evaluation team produced a web-based prototype of the BioCoRE Job Management Tool that incorporates features desired by users such as jobs based on prior jobs, sequential job submission, editable scripts, and easier views of job data. The BioCoRE Notebook is also a focus of prototype development, with a File Management Notebook component in early development as a complement to the successfully prototyped Presentation Notebook component.

BioCoRE for Training The Resource recognizes the vital importance of training towards the education and professional growth of young scientists. Consequently, in the last year, extending the training capabilities of BioCoRE has seen increased emphasis. A major development has been the new BioCoRE capability to create public project

areas (see p. 31). While until recently BioCoRE was organized around private projects only visible to to members of those projects, now any BioCoRE user may join a public project, making it easy for researchers to disseminate training materials within BioCoRE. This further facilitates broader interactions and discourse between experienced and novice researchers, and support training and mentoring activities.

BioCoRE In The News

- Tina Adler. *Collaboratories: Sharing Resources to Solve Complex Problems.* NCRR Reporter. Vol. 27, No. 1, pp. 4-7.[§]
- Jim Barlow. *Web-based collaboration links labs to supercomputers.* University of Illinois at Urbana-Champaign press release, September 3, 2002.[¶]

BioCoRE Posters/Presentations/Demos/Tutorials/Talks:

Posters:

- *BioCoRE: A Biological Collaborative Research Environment*, 2002 NCSA/Alliance All-Hands Meeting May, 2002

Presentations:

- *BioCoRE: A Collaboratory for Structural Biology*, Data and Collaboratories in the Biomedical Community Workshop Ballston, VA, September 16-18, 2002 (G. Budescu)
- *Collaboratory Evaluation: Beyond BioCoRE*, Data and Collaboratories in the Biomedical Community Workshop Ballston, VA, September 16-18, 2002 (G. Budescu)
- *BioCoRE: The Biological Collaborative Research Environment*, Access Grid presentation, NCSA, Champaign, IL, October 22, 2002 (R.Brunner and K. Vandivort)
- *BioCoRE: A Biological Collaborative Research Environment*, 10th International Conference on Intelligent Systems for Molecular Biology, Edmonton Canada. August 5, 2002 (K. Vandivort)
- BioCoRE demonstration, 10th International Conference on Intelligent Systems for Molecular Biology, Edmonton Canada. August 8, 2002 (K. Vandivort)

[§] `http://www.ncrr.nih.gov/newspub/jan03rpt/stories1.asp`

[¶] `http://www.news.uiuc.edu/scitips/02/0903biocore.html`

In the past year BioCoRE has been demonstrated 19 times using the Resource projection facility.

Scope of BioCoRE User Support Most BioCoRE support occurs on-line, through live chats in the BioCoRE control panel. A small amount of communication also occurs through email.

Links to BioCoRE (Google, April 2003): 31 Domains; 68 Sites; 70 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 us, periodic user surveys, and other evaluation methods, user interviews, and user meetings.

During March and April of 2003 we had contacted our users with VMD* (14,158 individuals), NAMD† (2,516 individuals) and BioCoRE‡ (165 individuals) surveys. The surveys are still ongoing, and we expect to analyze the responses and write three reports, one for each survey, this summer.

Lending out Expertise

Additional service activities the Resource staff is engaged in are:

- BioSoft DB
  The BioSoft DB§ is a catalog of structural biology-related programs created by developers around the world. The Resource opened it to the public in January 2001 and it already contains 344 programs, listed in 23 categories. In the past year it had 4,000 unique visits.

*`http://www.ks.uiuc.edu/Research/vmd/survey/survey2003.html`

†`http://www.ks.uiuc.edu/Research/namd/survey/survey2003.html`

‡`http://www.ks.uiuc.edu/Research/biocore/spring2003survey/txt/survey2003.html`

§`http://www.ks.uiuc.edu/Development/biosoftdb/`

- 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 one visitor and we expect to host six more this summer. Visitors typically fund their visits, and we supply the computing resources and knowledge. These visits are beneficial to all involved.

- 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 reliabllity of our products. Our user population keeps growing and consequently we are expected to invest more and more resources in user support. With over 30,000 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 next business day. Nontrivial inquiries may take longer, preferably no longer than three business days.

- The Resource is organizing an NSF-sponsored summer school on Theoretical and Computational Biophysics to be held June 2-13, 2003 (details available on p. 112)[¶]

- The Resource participated on March 14-15, 2003, in the Beckman Institute's open house in conjunction with the UIUC College of Engineering. The Resource presented a demonstration titled "Through the virtual looking glass", a journey portraying molecules of life in our 3D facility[‖]. The 174 visitors, students, faculty, and others showed a great interest in the work.

Seminars 1997–2002 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 Beckman 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 abstracts are all posted on our web site[**] for easy information retrieval. Below is the complete list of the Resource seminars in the past year:

Spring 2003

[¶] http://www.ks.uiuc.edu/Training/SumSchool03/

[‖] http://www.ks.uiuc.edu/Services/Meetings_Tutorials/Tutorials/OpenHouse2003/

[**] http://www.ks.uiuc.edu/Services/Seminar/

Tue, Jan 21, 2003 David Nelson, Harvard University, Cambridge, MA *Localized States and Biophysics*

Mon, Feb 3, 2003 Michael Boersch, Universitat Stuttgart, Germany *Stepwise Rotation of the Gamma-subunit of EfoF1 ATP Synthase During ATP Synthesis and Hydrolysis - A Single-molecule FRET Approach*

Mon, Feb 24, 2003 Kevin Y. Sanbonmatsu, Los Alamos National Laboratory, Los Alamos, NM *The Ribosome in Motion: Explicit Solvent Simulation of the 70S Ribosome*

Fri, Mar 7, 2003 Martin Engelhard, Max Planck Institute of Molecular Physiology, Dortmund, Germany *The Natronobacterium Pharaonis Sensory Rhodopsin II-NpHtrII Complex: From Retinal Isomerization to Transducer Activation*

Mon, Mar 17, 2003 Greg Voth, University of Utah, Salt Lake City, Utah *The Multi-Scale Simulation of Biomolecular Assemblies*

Mon, Apr 14, 2003 Michael Chapman, Florida State University, Tallahassee, FL *The Structure of Adeno-Associated Virus - a Vector for Human Gene Therapy*

Mon, May 5, 2003 Norbert Scherer, University of Chicago, Chicago, Illinois *Intermediates and Cooperativity in Single Molecules and Fibers*

Fall 2002

Mon, Sep 16, 2002 Taekjip Ha, University of Illinois, Urbana-Champaign, IL *Single-molecular Dynamics of Four-way Junctions in DNA and RNA*

Mon, Sep 23, 2002 Michael Klein, University of Pennsylvania, Philadelphia, Pennsylvania *Computer Simulation Studies of Biomolecules at Soft Interfaces: The Continuing Challenge of Bridging Length- and Time-scales*

Mon, Sep 30, 2002 Shigehiko Hayashi, University of Illinois at Urbana-Champaign, Urbana, Illinois *Molecular Mechanism of Spectral Tuning and Photoactivation in Retinal Proteins*

Mon, Oct 14, 2002 Nathan Baker, Washington University, St. Louis, Missouri *Investigating the Electrostatics of Nanoscale Bomolecular Systems*

Mon, Oct 21, 2002 Jose Onuchic, University of California at San Diego, La Jolla, California *Exploring the Protein Folding Funneling Landscapes: Connecting Minimalist Models and All-atom Calculations*

Mon, Oct 28, 2002 Jay X. Tang, Indiana University at Bloomington, Bloomington, Indiana *Physical Properties of Actin Assembly and Cell Motility*

Mon, Nov 4, 2002 Boris Martinac, University of Western Australia, Crawley, Australia *Gating of Mechanosensitive Channels by Bilayer Deformation Forces*

Mon, Nov 11, 2002 David A. Case, The Scripps Research Institute, La Jolla, California *Macromolecular Simulations Using Continuum Solvent Models*

Mon, Dec 9, 2002 Ka Yee Lee, University of Chicago, Chicago, Illinois *Lipid-Protein Interactions at Interfaces: From Alzheimer's Beta Amyloid Peptide to Poloxamer*

TRAINING

The Resource recognizes the vital importance of training towards the education and professional growth of young scientists. We have begun in the past 12 months to expand web-based training venues and a new training section on our site has been created*. The Resource is 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
- Off-site tutorials
- Classes
- Graduate student education
- Postdoctoral associate training

The Resource faculty is heavily involved in programmatic efforts and in steering the UIUC campus towards a greater offering of classes for graduate and undergraduate students in the areas of computational sciences and their applications in the biomedical fields and life sciences. A recent class, Biophysics of Membrane Proteins (BIOPHYS490M †), offered in Spring 2003, was funded by the Resource, held by E. Tajkhorshid, and dealt with the key role of life sciences in the future world of science and technology. The class explained questions, concepts, and challenges in the field of structure activity relationship of proteins to graduate students of Physics and Chemistry. Our faculty also participates in summer school initiatives bridging physical and life sciences as detailed below. We make our resources available to regular UIUC classes several times a year, and to rotation students from various departments.

Resource personnel (Prof. Schulten, Dr. Sener, Mr. Dittrich, Mr. Kanchanawarin) have taught on a voluntary basis a new class, Physics 1999PPP, on the physics of the human body, the class being taught in addition to the regular teaching of Professor Schulten. Physics 199PPP had freshmen from Physical Sciences, Life Sciences, and Engineering and introduced students through hands-on demonstrations, e.g., dissecting a cow's eye

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

†URL: `http://www.ks.uiuc.edu/Services/Class/BIOPHYS490M/`

or electron microscopy of bone, modern media, and conventional lectures to the human body as a physical machine. Topics covered included vision, hearing, skeleton, muscles, metabolism, peripheral and central nervous system. This is a new course and Resource personnel developed entirely new lecture material.

2003 Summer School [‡] The Resource is organizing an NSF-sponsored summer school on computational and theoretical biophysics to be held on June 2-13, 2003. The school will explore a wide range of physical models and computational approaches used for the simulation of biological systems and the investigation of their function at an atomic level. The course will be based on case studies including the properties of membranes, mechanisms of molecular motors, trafficking in the living cell through water and ion channels, signaling pathways, visual receptors, and photosynthesis. Relevant physical concepts, mathematical techniques, and computational methods will be introduced, including force fields and algorithms used in molecular modeling, molecular dynamics simulations on parallel computers, steered molecular dynamics simulations, and combined quantum mechanical - molecular mechanical calculations. The workshop is designed for graduate students and postdoctoral researchers in computational and/or biophysical fields who seek to extend their research skills to include computational and theoretical expertise, as well as other researchers interested in theoretical and computational biophysics. Theory sessions will be followed by hands-on computer labs in which students will be able to set up and run simulations.

Summer school instructors include L. Kale (UIUC), M. Klein (U. Penn), I. Kosztin (U. Missouri), T. Martinez (UIUC), T. Schlick (NYU), K. Schulten (UIUC), Z. Schulten (UIUC), R. Skeel (UIUC), and E. Tajkhorshid (UIUC). The school program is appended (App. A).

The school announcement has attracted a wide interest and of the over 220 applicants, 90 have been accepted.

Training on the Web [§] The new training section on our site includes tutorials using Resource tools, links to relevant classes and to other online teaching tools, useful in developing teaching contents and techniques within the Resource. This page is regularly updated as the Resource explores new strategies for online training. The Resource has given numberous demonstrations of NAMD, VMD, and BioCoRE in the past year, and is engaged in developing science tutorials. A relevant training development has been the new BioCoRE capability to create public project areas (see p. 31). While until recently

[‡]URL: `http://www.ks.uiuc.edu/Training/SumSchool03/`

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

BioCoRE had been organized around private projects only visible to members of those projects, now any BioCoRE user may join a public project, making it easy for researchers to disseminate training materials within BioCoRE. This further facilitates broader interactions and discourse between experienced and novice researchers, and supports training and mentoring activities. On the main BioCoRE server, for example, we have added a public "BioCoRE Help" project to help new users with any problems they may have. Future training plans include adding the Resource's 2003 Summer School material to the web, updating the BioCoRE tour, creating tutorial tools within BioCoRE, and offering continuous demos and tutorials.

Tutorials Formal Resource tutorials in the past year include:

- NAMD and VMD at SC2002, November 18-22, 2002
- BioCoRE seminar via the Access Grid October 2002.
- BioCoRE session at the 10th International Conference on Intelligent Systems for Molecular Biology, Edmonton, Canada, August 2002.
- JMV, VMD, and BioCoRE sessions with Sun Microsystems at Siggraph, July 23-25, 2002

We offer online tours for BioCoRE and brief tutorials for VMD. More information on both workshops and other training opportunities organized by the Resource are posted on our web site ¶.

Internal Resource tutorials are offered regularly on an as-needed basis, featuring sessions on the use of software development tools by scientists. Our web pages offer 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, web design and implementation. We are developing now a special *tool page* outlining the various tools we use in ourn development efforts. This page will be available to the public.

Resource Library In the past year, we have purchased over 40 new books that expand our well stocked Resource library. In addition to the UIUC library's collection of journals, online and hard-copy, we continue to subscribe to the following journals:

- Science

¶URL: `http://www.ks.uiuc.edu/Services/Meetings_Tutorials/Tutorials/`

- Nature
- Physik Journal
- SysAdmin
- C/C++ Users Journal
- Chronicle of Higher Education

Graduates Recent UIUC graduates and postdoctoral associates who received their training at the Resource are:

PhD Recipients

- Alexander Balaeff
  Ph.D., Biophysics, University Of Illinois, Fall 2002
- James Phillips
  Ph.D., Physics, University Of Illinois, Fall 2002

Postdoctoral Associates

- Shig Hayashi (4/2001-3/2003)

Visitors The Resource has continued its visitor program. While here, the visitors, who come with their own support, receive "on-site" training. They learn how to use the Resource software and other packages available on the Resource's powerful computers, benefit from the expertise and knowledge of Resource members, and bring back to their home laboratories critical skills and new experiences.

This effort-intensive initiative, while quite taxing on Resource members, offers practical and most useful education to the visitors and serves as a vehicle for transferring knowledge and know-how back to the biomedical community. In the past year we had one visitor, Grischa Meyer, Physics, U West Australia (September, 2002). We expect six visitors during the Summer of 2003.

Training Collaborations We have started to work with the World University Network (WUN) exchange program and expect to host this summer a biophysics student from York, UK. The program fosters international interactions between students and senior researchers in the field.

Manuals and Tours Our software manuals have been available on the web for many years, and are regularly updated. BioCoRE has established a new training concept which combines an online tutorial with a slide tour. The 'tour' is regularly updated and developed [‖]. The NAMD team has adopted a similar solution [**].

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

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

DISSEMINATION

The Resource's dissemination and outreach efforts have greatly intensified in the past year, 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 in the past year 22 papers in prestigious journals. The Resource's website won a 2003 UIUC Webmasters Forum Cool Site Award, a cover story on the BioCoRE environment was featured in the NIH/NCRR Reporter magazine, and press releases and other stories have been published (all detailed below). Resource personnel presented talks and posters in professional meetings.

Stories on the Resource appeared in stories in popular media and these news-making stories are posted on the Resource web site in the "In the News" section*:

- April 9, 2003 - TCB Wins Cool Site Award
  `http://www.webmasters.uiuc.edu/coolSites2003.asp`
- March 10, 2003 - Collaboratories Sharing Resources to Solve Complex Problems
  `http://www.ncrr.nih.gov/newspub/jan03rpt/stories1.asp`
- December 5, 2002 - PSC's LeMieux Enables Award-Winning Science
  `http://www.psc.edu/publicinfo/news/2002/sc_2002-12-05.html`
- December 4, 2002 - Illinois' NAMD code among the winners at the Olympics of supercomputing
  `http://www.news.uiuc.edu/scitips/02/1204namd.html`
- December 2, 2002 - When the Sims Meet the Cells
  Business Week, 12/2/2002 Issue 3810, p105, 1/4p, 1c
- November 21, 2002 - SC2002 Conference Concludes by Smashing Attendance Records, Rewarding Successes in High Performance Computing and Networking
  `http://access.ncsa.uiuc.edu/Releases/11.21.02_SC2002_Con.html`
- November 7, 2002 - SC2002 Gordon Bell Awards to Highlight Unprecedented HPC Accomplishments
  `http://www.ncsa.uiuc.edu/News/Access/Releases/02Releases/11.07.02_SC2002_Gor.html`
- September 30, 2002 - Precious Bodily Fluids
  `http://www.psc.edu/science/schulten2002.html`

*URL: `http://www.ks.uiuc.edu/Publications/stories.shtml`

- September 3, 2002 - Web-based collaboration links labs to supercomputers
  `http://www.news.uiuc.edu/scitips/02/0903biocore.html`
- June 2, 2002 - This Dance is in us all
  `http://www.news-gazette.com/story.cfm?number=11700`

Publications

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

- 22 refereed articles (see below)
- Over 45 talks (PIs and other members as specified below)
- 8 posters

Following are the total numbers of resulting publications for the entire funding cycle 1999-2002 by BTA unit, as well as a detailed listing of the past year's papers and presentations.

BTA unit: (C)

Total for the last year (2002-2003):

PUBLISHED:
Books: 0 Papers: 5 Abstracts: 0

IN PRESS OR SUBMITTED:
Books: 0 Papers: 3 Abstracts: 0

PUBLISHED:

- M. V. Bayas, K. Schulten, and D. Leckband. *Forced detachment of the CD2-CD58 complex*. Biophys. J., 84:2223-2233, 2003.
- R. Braun, M. Sarikaya, and K. Schulten. *Genetically engineered gold-binding polypeptides: Structure prediction and molecular dynamics*. Journal of Biomaterials Science, 13:747-758, 2002.
- J. Ervin, E. Larios, S. Osvath, K. Schulten, and M. Gruebele. *What causes hyperfluorescence: folding intermediates or conformationally flexible native states?* Biophys. J., 83:473-483, 2002.
- M. Gao, D. Craig, V. Vogel, and K. Schulten. *Identifying unfolding intermediates of FN-III10 by steered molecular dynamics*. Journal of Molecular Biology, 323:939-950, 2002.
- M. Gao, M. Wilmanns, and K. Schulten. *Steered molecular dynamics studies of titin I1 domain unfolding*. Biophys. J., 83:3435-3445, 2002.

IN PRESS OR SUBMITTED:

- R. Amaro, E. Tajkhorshid, and Z. Luthey-Schulten. *Developing an energy landscape for the novel function of a $(\alpha/\beta)_8$ barrel: Ammonia conduction through HisF.* Proc. Natl. Acad. Sci. USA, In press, 2003.
- A. Aksimentiev, I. Balabin, R. H. Fillingame, and K. Schulten, *Insights into the Molecular Mechanisms of F_0 ATP Synthase Operation*, Proc. Natl. Acad. Sci. USA, 2003. Submitted.
- D. Craig, M. Gao, V. Vogel, and Klaus Schulten. *Modulating mechanical stability of fibronectin type III modules through variations in amino acid sequence.* Structure, 2003. Submitted.

BTA unit: (C, D, & T)

Total for the last year (2002-2003):

PUBLISHED:
Books: 0 Papers: 4 Abstracts: 0

NUMBER IN PRESS OR SUBMITTED:
Books: 0 Papers: 3 Abstracts: 0

PUBLISHED:

- (C & T) M. Ben-Nun, F. Molnar, K. Schulten, and T. J. Martinez. *The role of intersection topography in bond selectivity of cis-trans photoisomerization.* Proceedings of the National Academy of Sciences, USA, 99:1769-1773, 2002.
- (C & T) M. K. Sener, D. Lu, T. Ritz, S. Park, P. Fromme, and K. Schulten. *Robustness and optimality of light harvesting in cyanobacterial photosystem I.* Journal of Physical Chemistry B, 106:7948-7960, 2002.
- (C & T) E. Tajkhorshid, P. Nollert, M. O. Jensen, L. J. W. Miercke, J. O'Connell, R. M. Stroud, and K. Schulten. *Control of the selectivity of the aquaporin water channel family by global orientational tuning.* Science, 296:525-530, 2002.
- (T & C) M. Gao, H. Lu, and K. Schulten. *Unfolding of titin domains studied by molecular dynamics simulations.* Journal of Muscle Research and Cell Motility, 23:513-521, 2002.

IN PRESS OR SUBMITTED:

- (C & T) A. Balaeff, L. Mahadevan, and K. Schulten. *Modeling DNA loops using the theory of elasticity.* Phys. Rev. E, 2003. Submitted.
- (T & D) E. Tajkhorshid, A. Aksimentiev, I. Balabin, M. Gao, B. Isralewitz, J. C. Phillips, F. Zhu, and K. Schulten. *Large scale simulation of protein mechanics and function.* In David Eisenberg and Peter Kim, editors, Advances in Protein Chemistry. Elsevier, 2003. In press.
- (C & T) A. Balaeff, L. Mahadevan, and K. Schulten. *Structural model for cooperative DNA binding by CAP and lac repressor.* Proc. Natl. Acad. Sci. USA. Submitted.

BTA unit: (S)

Total for the last year (2002-2003):

PUBLISHED:
Books: 0 Papers: 0 Abstracts: 0

IN PRESS OR SUBMITTED:
Books: 0 Papers: 0 Abstracts: 0

PUBLISHED: None

IN PRESS OR SUBMITTED: None

Software Releases (2002-2003)

- VMD:
  - v1.8 on 10 Dec 2002
  - v1.8.1 in May 2003
- NAMD:
  - v2.5b1 on 18 Apr 2002
  - v2.5b2 and v2.5 in May 2003
  - overall redesign and initial release of NAMD3 by December, 2003.
- BioCoRE: Incremental updates every few weeks[†]

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

BTA unit: (T)

Total for the last year (2002-2003):

PUBLISHED:
Books: 0 Papers: 13 Abstracts: 0

IN PRESS OR SUBMITTED:
Books: 0 Papers: 14 Abstracts: 0

PUBLISHED:

- S. Hayashi, E. Tajkhorshid, and K. Schulten. *Structural changes during the formation of early intermediates in the bacteriorhodopsin photocycle.* Biophys. J., 83:1281-1297, 2002.
- L. V. Kale. *The Virtualization Approach to Parallel Programming: Runtime Optimizations and the State of the Art.* Proceedings of LASCI 2002 (Los Alamos Computer Science Institute), Santa Fe, NM, October 2002.
- L. V. Kale, S. Kumar, and J. DeSouza. *A Malleable-Job System for Timeshared Parallel Machines.* Proceedings of the 2nd IEEE/ACM International Symposium on Cluster Computing and the Grid (CCGrid 2002), Berlin, Germany, May 2002.
- O. S. Lawlor and L. V. Kale. *A Voxel-Based Parallel Collision Detection Algorithm.* Proceedings of the 2002 International Conference on Supercomputing (ICS2002), ACM Press, pp. 285-293, New York, June 2002.
- Q. Ma, J. Izaguirre, and R. D. Skeel. *Verlet-I/r-RESPA is limited by nonlinear instability.* SIAM J. Sci. Comput., 2003, In press.
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Talks

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

Klaus Schulten

- August 17-21, 2002. Protein Society Meeting, San Diego, CA. *The Mechanical Functions of Proteins*
- August 20-24, 2002. 10th International Conference on Retinal Proteins, Seattle, WA. *Spectral Tuning and Photodynamics in Visual Receptors*
- September 7-12, 2002. EURESCO Conference on "Computational Biophysics: Integrating Theoretical Physics and Biology". San Feliu du Guixois, Spain. *Physics of Photosynthetic Units in Purple Bacteria*
- September 27-29, 2002. APS Workshop Opportunities in Biology for Physicists, Boston, MA, *Membrane Proteins in Action*
- September 30- October 2, 2002. US/UK Meeting on High Performance Computing, UK. *Large Scale Simulation of Membrane Protein Funtion"*
- October 9, 2002. Biophysics School, Bad Honneff, Germany. *Immunoglobulins and Fibronectins - Essential Proteins for the Mechanics of Cells*
- November 26, 2002. Lawrence Berkeley National Laboratory, Life Sciences Divisionr, Berkeley, CA. *Membrane Proteins in Action as Seen by in situ Molecular Dynamics Simulations*
- April 4, 2003. Purdue University Computing Research Institute Seminar, West Lafayette, IN. *Large Scale Simulation of Membrane Protein Function*
- April 15-21, 2003. Symposium. Frankfurt Institute for Advanced Studies, Frankfurt, Germany. *Quantumbiology*
- April 26-30, 2003. DFG Research Center, Berlin, Germany *Computational Modeling of the Mechanics of Living Cells*
- June 15-20, 2003. Gordon Conference on Membrane Proteins, Plymouth, NH *Title to be finalized later*
- June 22-27, 2003. Gordon Conference on Photosynthesis, Bristol, RI cbhkml@aol.com *Title to be finalized later*

Gila Budescu

- September 16, 2002. *BioCoRE: A Collaboratory for Structural Biology.* Data and Collaboratories in the Biomedical Community, Ballston, Virginia.
- September 16, 2002. *Collaboratory Evaluation: Beyond BioCoRE.* Data and Collaboratories in the Biomedical Community, Ballston, Virginia.

Laxmikant Kale

- February 27 - March 1 2003. *Molecular Simulations on Parallel Machines via Faucets, a Grid Scheduler.* Experiments and Simulations at Nano-Bio Interface and Frontiers of Grid Computing, Louisiana State University, Baton Rouge, Louisiana.

Robert Skeel

- May 2002. *Dynamics of Proteins on a Continuous Energy Landscape*, Lyon, France.
- Jun 2002. Conference on Scientific Computation, Geneva, Switzerland.
- Oct 2002. Applied Math Seminar, University of Michigan, Ann Arbor.
- Nov 2002. *Molecular Modeling and Computation: Perspectives and Challenges*, Pasadena, CA.

Other Resource members gave the following talks and poster presentations in the past year:

- May 2002. 2002 Alliance All-Hands Meeting, NCSA, Urbana, IL. (James Phillips, Kirby Vandivort, Robert Brunner, Tim Skirvin)
- May 2002. Scaling to New Heights Workshop, Pittsburgh Supercomputing Center. *NAMD: Biomolecular Simulations of Thousands of Processors.* (James Phillips)
- May 2002. CCGrid2002 Conference, Berlin, Germany. (Sameer Kumar)
- July 2002. Gorden Research Conference on Computational Chemistry, Colby-Sawyet College, New Londo, NH. *Computational Chemistry for Membrane Channels.* (Emad Tajkhorshid)
- July 2002. SIGGRAPH 2002 Conference, San Antonio, TX. (John Stone and Michael Bach)

- August 2002. 10th International Conference on Retinal Proteins, Seattle, WA. (Emad Tajkhorshid)
  - Poster: *Molecular dynamics simulation of early events in the activation of rhodopsin.*
  - Poster: *Structural changes during the formation of early intermediates in the bacteriorhodopsin photocycle.*
  - Poster: *Spectral tuning and photoisomerization dynamics of retinal in rhodopsin studied by ab initio quantum mechanical/molecular mechanical calculations.*
- August 2002. 11th Symposium on Theoretical Chemistry, Aichi, Japan. (Shigehiko Hayashi)
- August 2002. ISMB 200 Conference, Edmonton, Alberta, Canada. (Gila Budescu and Kirby Vandivort)
- September 2002. Edward Tifte Graphic Press LLC Course, Chicago, IL. (Chalermpol Kanchanawarin)
- September 2002. Scientific Python Conference, UCSD/Scripps Research Institute, Pasadena, CA. (Justin Gullingsrud)
- October 2002. Femtochemistry and femtobiology Conference, European Science Foundation, Antalya, Turkey. (Melih Sener)
- October 2002. Cell & Molecular Biology Molecular Biophysics Research Symposium, UIUC, Urbana. (Emad Tajkhorshid and C. Kanchanawarin)
- October 2002. Second Annual Computational Chemistry Conference, University of Kentucky, Lexington, KY. (Emad Tajkhorshid)
- November 2002. LISA '02 – 16th Systems Administration Conference and Exhibition, Philadelphia, PA. (Tim Skirvin)
- November 2002. Supercomputing '02 Conference, Baltimore, MD. (Laxmikant Kale, Jim Phillips, Sameer Kumar)
- November 2002. Molecular Modeling and Computation workshop at Cal Tech; Modeling and Simulation for Materials, UCLA, CAs. (David Hardy and Wei Wang)
- November 2002. Gen ProE 2003, Tokyo, Japan. (Shigehiko Hayashi)
- February 2003. Sanibel Symposium, St. Augustine, FL. (Emad Tajkhorshid)

- February 2003. Biophysical Society meeting, San Antonio, TX. (Emad Tajkhorshid, Rosemary Braun, Elizabeth Villa, Fangqiang Zhu, Justin Gullingsrud, Deyu Lu, Oleksii Aksimentiev, Mu Gao, Melih Sener, Markus Dittrich, Chalempol Kanchanawarin)
- February 2003. Nanotech 2003 Conference, San Francisco, CA. (Ilya Balabin)
- April 2003. IPDPS 2003, International Parallel and Distributed Symposium, Nice, France. (Sameer Kumar)
- April 2003. Department of Physics Condensed Matter and Biological Physics Seminar, Purdue University, West Lafayette, IN. (Aleksei Aksimentiev)
- May 2003. Department of Molecular and Integrative Physiology Seminar, UIUC. (Emad Tajkhorshid)
- May 2003. 2003 Alliance All-Hands Meeting, NCSA, Urbana, IL. (James Phillips, Kirby Vandivort, Robert Brunner, Tim Skirvin)
- June 2003. Gordon Conference on ATP Synthase, New Hampshire (Aleksei Aksimentiev)

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 (132)
- Major sites that use our images
- Others publish our images
- On-site demonstrations
- Remote demonstrations
- Annual Open House events (over 160 visitors on the average)

A recent Google search yielded the following statistics regarding links to the Resource site: 270 pages link to our site, from 253 sites in 94 domains.

There have been a total of 299,659 unique visitors to the Resource web site, an average of 21,704 per month, over the last year. The sections most visited are listed below:

	Total Visitors	Visitors per Month
VMD	109,200	11,554
NAMD	43,066	4,669
BioCoRE	20,015	2,001
Other Research	65,513	6,686
Papers	25,029	2,612
galleries	13,246	1,290
seminars	2,735	347
Biosoft DB	3,978	425

Numbers from Apr 2002 - Mar 2003

The Resource responds to 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[‡].

Licensing and Distribution

As an important component of our dissemination efforts we have continued in the past year to enhance our distribution mechanism for papers, software, and other knowledge and expertise. We are in an ongoing discussion on improving the copyright protection of our published materials, we develop new licenses as needed— the most recent one was the BioCoRE server license— and we explore ways to make the adoption, licensing, and installation of our tools by individual and institutional users easy and simple.

Finally, our commitment to improving our dissemination efforts have lead in the past year to further additions on our site, most notably:

- Poster Gallery
- Revamped VMD Gallery
- Seminar database
- Registration database (for 2003 summer school; code will be reused for similar events)

In the coming year we intend to maintain the above efforts and to proceed with renewing the Resource brochures, providing new tutorials, revising our paper download procedures, developing a new talks database, expanding our web site, and more.

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

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