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Introduction

The NIH Resource for Macromolecular Modeling and Bioinformatics, in collaboration with experimental laboratories in universities, research institutions and industry across the U.S. and around the world, explores the physical mechanisms underlying the biomolecular processes in living cells. For this purpose it develops efficient software that facilitates the analysis, modeling and visualization of the molecular apparatus in biological cells and makes these tools freely available to laboratories where biomolecular aggregates are discovered and measured. In particular, the Resource develops molecular modeling tools which can integrate structural information with bioinformatics databases and molecular dynamics simulations; provides high performance molecular visualization and simulation software, capable of modeling biomolecules in realistic environments of 100,000 atoms or more; advances the conceptual and methodological foundations of molecular modeling in the fields of quantum biology, mechanobiology, and interactive modeling; supports the entire biomedical research process through a web-enabled collaborative environment; and, finally, enhances training and dissemination by leveraging web-based molecular graphics and integrated modeling technologies.

Summary of Research Progress

During the past five year funding period of the Resource, life science research has been almost completely transformed. With the sequencing of the genomes of many organisms, in particular that of man, there has emerged a new view of organisms as a networked system of metabolic and signaling pathways. Today, organisms and cells are approached as a healthy functioning whole; studies of disease and therapy focus on failure and repair of pathways. The computer has become an indispensable instrument of all researchers confronted with the vast new data and their integration.

However, the same data remind biomedical scientists that for most proteins structures, functions, mechanisms, and pathways are still elusive, and that Science needs to make a strenuous, concerted effort to gain this missing knowledge.

Proteins, the products of genomes, can only be completely understood in the context of their cellular environment. One must not lose sight of the fact that the genome only partly defines a cell; Virchow's famous 19th century statement,"It takes a cell to make a cell," is still true today. This forces modelers to embed proteins in their proper cellular environment (e.g., membranes and water) to study function and resolve mechanisms. Including the cellular environment is always computationally costly, but the dramatic

The preparation of this report was coordinated by Ilya Balabin

increase of computing power makes this feasible today. In fact, the Resource has already completed numerous molecular dynamics studies of proteins in membrane environments, the most recent one including 106,000 atoms for the overall system.

The increase in computing power is reflected in the tremendous increase of computational resources available at the national supercomputing centers. In the year 2001 the centers have seen a ten-fold increase in their capacity through the acquisition of parallel computers with over one thousand processors. The computer time awarded to the Resource reflects this trend; its awards have increased steadily over the years 1994-2001, but most dramatically during the last three years, namely more than tenfold. This opportunity for biomedical science poses a great challenge for computational scientists to harness thousands of parallel processors in their modeling. The Resource is in an extremely fortunate situation in this regard, having focused for a decade on the necessary development. The Resource molecular dynamics program NAMD runs the most advanced simulations (full electrostatics and control of ambient pressure) on 1000 processors with unsurpassed efficiency on the largest machine available to biomedical researchers today (at the Pittsburgh Supercomputing Center).

Commodity computing in the form of desktop machines and free operating systems (e.g., Linux) is advancing rapidly as well. As long as one limits processor numbers, presently to about 32, one can connect clusters of workstations through commodity networks, resulting in extremely powerful, cost-effective machines. The Resource has employed cluster computing since 1993 and shared its expertise in hands-on workshops with a wide community. Molecular dynamics calculations that required 100 processors on a multi-million dollar Cray T3E just two years ago can now be performed on a $25,000 PC-cluster installation. Making this source of computing power immediately available to biomedical researchers makes revolutionary molecular modeling tools ubiquitous in biomedicine.

The Resource has facilitated modeling in part through its development of advanced molecular graphics. Until recently, this technology was confined to specialized workstations with $10,000 price tags. Computer game technology and a commitment by the Resource to develop VMD for personal computers without sacrificing high standards, have made it possible for an investment of a few hundred dollars to turn a PC into an advanced molecular graphics workstation capable of viewing systems of 100,000 atoms or more with stereo graphics and a six-dimensional input device. VMD on Windows, Mac OS X, Linux and Unix has several thousand users today.

VMD and NAMD were designed to work together, making it possible to view biomolecules with thousands of atoms as they are simulated. The main advance in this approach called Interactive Molecular Dynamics (IMD) lies in the opportunity to interact with the model. VMD and NAMD together comprise a dynamic macromolecular model kit with high fidelity interactions, inviting the user to immediately explore any hypothetical molecular

mechanism.

In fact, one of the key goals of the Resource is to turn molecular modeling into an engaging, widely used tool. The increasing availability of protein structures will lead to most biomedical researchers using structural information for the design and analysis of experiments; increasingly, researchers will also want to investigate hypotheses through their own molecular modeling. Until now, such modeling came at a steep price, most of it paid up front when a molecular dynamics run had to be set up with the help of nearly impenetrable structure and force field parameter files. NAMD and VMD incorporate tools that automate this process as much as possible.

Computational steering of molecular models has been realized just when experimentalists made the corresponding breakthrough, manipulating single molecules through atomic force microscopes and optical tweezers as well as observing single molecules spectroscopically. This coincidence has led to extremely fruitful research at the Resource since modeling was needed to complement experiments: the latter provide only limited information on molecular properties, e.g., on simple geometrical characteristics and on forces that rupture the binding of substrates, unfold proteins, or turn molecular motors like that of F-ATPase. To relate the observed mechanics to the architecture of proteins is the domain of so-called steered molecular dynamics (SMD) simulations, pursued with great success by the Resource and its many collaborators, together contributing to the founding of the new field of mechanobiology, which studies the role of forces in cellular processes. Here forces appear as key ingredients of processes in cells: as substrates that drive reactions, as products of molecular motors, and as signals, mediated, for example, through integrins from the cellular matrix into the cell interior.

The Resource has coordinated an intense two-year effort of computer scientists, life scientists, and social scientists that designed and built a group-ware tool called BioCoRE for biomedical researchers. The tool, an incredible achievement for such a short time, permits scientists to form project groups that share and jointly work with many types of data on a platform-independent basis through web browsers. For example, scientists can submit modeling calculations through the web and jointly monitor the running calculations from a distance, with all related project data available at the click of a mouse. Researchers at different sites can simultaneously view and manipulate molecular graphics and interactive modeling sessions. BioCoRE, just completed and now being deployed for wide use, will enhance the productivity of biomedical researchers as an easy to use communication instrument, reducing the need for travel. BioCoRE is also ideal for training and teaching and as such has already been employed successfully in hands-on workshops taught by the Resource.

BioCoRE will serve the many collaborations that are supported by the Resource. During the past funding period, many collaborations have been completed, eleven of which led

to joint publications. Ongoing collaborations include an effort to model energy transduction in ATPase, involving at present a simulation of a 327,000 atom subsystem, studies of several membrane channels, for example the mechanosensitive channel MscL gated through membrane tension and aquaporins, for which the work identified a key mechanism for selective water transport. Other systems being investigated in collaborations are visual receptors, a large photosynthetic membrane protein (PS1), protein building blocks in micelles, and proteins that bind selectively to gold surfaces for bioengineering applications.

The Resource has a strong tradition in training, service, and dissemination, having developed, fine-tuned and extensively utilized its web site for all three purposes. The web site at `http://www.ks.uiuc.edu` is visited, on average, about four hundred times each day and has an average data volume of 450 MB of downloads per day, i.e., serving each visitor 1 MB of data on average. The Resource's widely popular web site offers its software, manuals and tutorials, publications and reports, and science highlights.

With a superb staff and gifted students; with innovative, world-class computational biology software and its wide user base; with an exemplary computational laboratory; with a world renowned and productive research program that produced over 140 publications during the past funding period; with vigorous collaborations that opened new research areas; with exemplary training, service, and dissemination efforts supported by a highly frequented web site, the Resource has maintained its leading role in computational life sciences.

Aquaporins: Selective Water Traffic Pathways

Water is the main component of life. It constitutes the major part, sometimes more than 98%, of all living organisms. Naturally, all living cells need to regulate their water contents precisely, and continuously. However, the cell membrane, mainly composed of lipids, does not provide enough capacity for the exchange of high volumes of water between the cytoplasm and the cell environment. Aquaporins *(AQPs), a family of recently discovered membrane proteins, are water channels designed for solving the problem of water traffic across the membrane by facilitating the passive, but very efficient, permeation of water.

These channels are widely distributed in all kingdoms of life, including bacteria, plants, insects, and vertebrates [1], and play critical roles in the cell water homeostasis. During the last decade, more than 50 different types of AQPs have been discovered in plants. In the human body, ten different AQPs have been characterized so far. These proteins are distributed in such organs as the eye, lung, RBC, CNS, salivary glands, and kidney. In the human kidney, three different AQPs, located in the proximal tubules and the collecting ducts, are used to reabsorb several hundred liters of water from urine to blood in an adult person every day. Despite the short term of AQP research, several diseases, such as congenital cataracts, Sjorgen's syndrome, and nephrogenic *diabetes insipidus*, have been found to be connected to the impaired function of these channels [1].

A subfamily of AQPs, known as aquaglyceroporins, have been specialized through evolution for importing small linear sugar molecules, such as glycerol, into the cell [2]. The E. coli glycerol uptake facilitator (GlpF) [3] is the most studied member of this subfamily and is essential for the normal growth rate of the bacterium when not enough carbon resources are available. Very recently, the importance of the dual functionality of aquaglyceroporins was also demonstrated in *Plasmodium falciparum*, the malaria parasite, which takes advantage of these channels both to face the osmotic changes during kidney passage and for its massive biosynthesis of glycerolipids during its development in the blood-stage [4].

AQPs form tetramers in the cell membrane. After the publication of two electron microscopy structures of human aquaporin-1 (AQP1) with medium resolution [5, 6], the first high resolution x-ray crystal structures of two aquaporins, GlpF [7] and AQP1 [8], enabled us to study these channels in atomic detail by molecular dynamics (MD) simulations, which resulted in several discoveries regarding the dynamics and function of AQPs.

Our MD simulations on AQP1 and GlpF in membrane described the formation of a single file of water inside the channel and revealed the critical role of a highly conserved region,

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

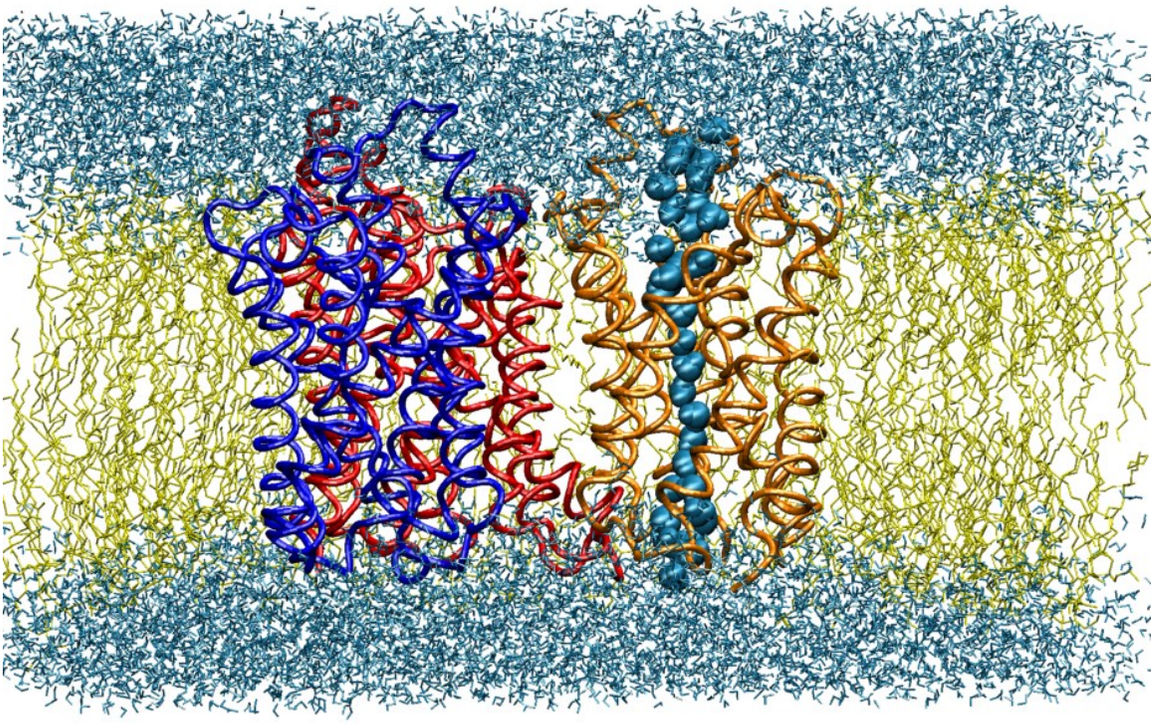

Figure 1: Transmembrane passage of water molecule through aquaporins. The simulated system includes the tetrameric protein (one monomer is hidden to improve the view), lipid bilayer, and water molecules on the two sides of the membrane (total 106,000 atoms). Water molecules form a single file inside the channel (shown only for one monomer) during their movement

the NPA motifs, in the stability and function of the channel [9,10]. Moreover, the complete pathway of substrate conduction in the channel was characterized. Analysis of hydrogen bond interactions of the substrate with the interior of the channel also explained for the first time why these channels incorporate in their architecture two characteristic loops, including energetically unfavorable secondary structure elements, which are conserved in the whole aquaporin family [10]. Then, by the application of a methodology known as steered molecular dynamics (SMD) [11], in which the studied event is accelerated via external forces, in order to overcome the problem of time scale, we successfully described the energy profile that a substrate molecule experiences during its passage through the channel [12]. The calculated free energy profile captures major binding sites and barriers in the channel in close agreement with the results of MD simulations [10] and the positions found in the crystal structure [7]. Moreover, it displays a pronounced asymmetry in its shape, suggesting for the first time that the asymmetric structure of the protein may be functionally important for an efficient uptake of nutrient molecules from the environment.

A remarkable functional property of all AQPs is their blocking mechanism against the transport of ionized species, including protons, through their water pores. Particularly paradoxical in this regard is the proton transport event, which is expected to be possible,

and even facilitated, through the water file formed inside the channel. This property is essential for the conservation of membrane's electrochemical potential, especially in those cells that use the proton gradient across the membrane as an energy source for ATP synthesis [13]. In a collaboration with the group of R. Stroud (UCSF), we addressed this problem through a combined experimental and theoretical approach. Several nanoseconds simulation of the wild-type GlpF and a mutant designed for higher water permeability resulted in very close permeability coefficients to those obtained experimentally. In both experiments and calculation an increase of about 30-40% in the water permeation was found for the mutant species, compared to that of the native form. Furthermore, the simulations have also provided new insight into the mechanism underlying the fascinating property of proton exclusion. Water molecules passing the channel are forced, by the protein's electrostatic forces, to flip at the center of the channel, thereby breaking the alternative donor-acceptor arrangement that is necessary for proton translocation [14].

In order to provide a closer link between simulations and experiments, a new technique was devised by which for the first time one can apply different hydrostatic pressures at the two sides of the simulated membrane, exactly in the same way that experiments are done [15]. Using this methodology, the water permeability coefficient calculated for GlpF at different pressure gradients was found to be linearly correlated to the applied pressure [15]

NAMD: Scalable Molecular Dynamics Software

NAMD* is a parallel, object-oriented molecular dynamics code designed for high performance simulation of large biomolecular systems [16]. NAMD employs the prioritized message-driven execution capabilities of the Charm++/Converse parallel runtime system,† allowing excellent parallel scaling on both massively parallel supercomputers and commodity workstation clusters.

NAMD's unique parallel scalability for biomolecular simulations has grown by two orders of magnitude during the grant period, from 8–16 processors in 1997 to 512–1024 processors today. Furthermore, today's processors themselves are a factor of four faster than those available in 1997, the NAMD source code is more efficient, and the modern simulation runs with full electrostatics. Continuing enhancements, particularly to the parallelization of the highly efficient particle mesh Ewald full electrostatics algorithm, have allowed 327,000 atom simulations of ATP synthase to run with 63% efficiency on 1024 processors of the recently available Lemieux Alpha cluster at the Pittsburgh Supercomputing Center.‡ NAMD performance on recent platforms for a smaller, more typical simulation with full electrostatics is presented in Figure 2.

NAMD now provides a wide range of simulation methods, including constant pressure and temperature dynamics, conformational and alchemical free energy perturbation, and a variety of steering methods. In particular, a simulation may be steered interactively via a network connection to VMD and a haptic interface device, an application which benefits greatly from increased simulation speed. NAMD incorporates the Tcl scripting language, which allows the user to implement new simulation protocols without recompiling.

NAMD was originally designed to complement the capabilities of the modeling program X-PLOR [17] by providing an efficient, parallel simulation engine. The initial X-PLOR file compatibility has been extended to include CHARMM [18], AMBER [19], and GROMACS [20] input files as well. In response to user demand for an alternative to these existing packages, the psfgen utility has been created for generating molecular structures from standard PDB coordinate files and the topology definitions supplied with the CHARMM force field. This utility has been incorporated into VMD, and extended to provide an increasingly complete simulation setup environment.

NAMD has had eight major public releases, starting with version 1.3 in July 1995 and continuing through versions 1.4, 1.5, 2.0, 2.1, 2.2, and 2.3 to the most recent, 2.4, released in March 2002. NAMD is distributed free of charge via the web as both source

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

†URL: `http://charm.cs.uiuc.edu/`

‡URL: `http://www.psc.edu/machines/tcs/lemieux.html`

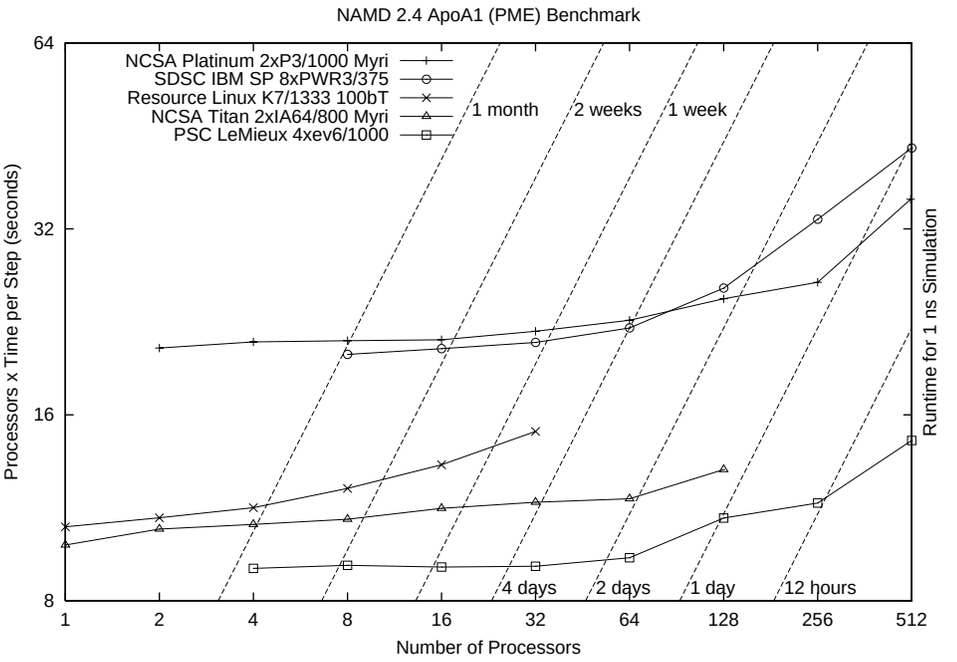

Figure 2: Total resources consumed per step for 92K atom benchmark on a variety of computational platforms by NAMD 2.4 on varying numbers of processors. Perfect linear scaling is a horizontal line. Diagonal scale shows absolute performance.

code and convenient precompiled binaries for eleven platforms, including massively parallel supercomputers, workstation clusters, and personal computers running Microsoft Windows, Linux, or Mac OS X. NAMD has over 3600 registered users (over 500 of whom are NIH-funded), who have downloaded the program over 5000 times during the past year alone. NAMD is also distributed with the Scyld Beowulf advanced Linux cluster operating system and is installed at the three NSF supercomputer centers (PSC, NCSA and SDSC).

In August 2001, Resource members presented a three-day NAMD workshop "Methods and Applications of Molecular Dynamics to Biopolymers," sponsored and hosted by the Pittsburgh Supercomputing Center. Comments and reviews from the 22 participants were excellent. In April 2002, a similar workshop "Biomedical Applications of Molecular Dynamics on the TeraGrid," was presented at the National Center for Supercomputing Applications for 93 participants from 26 institutions. Only 32 participants were present locally; the remaining 61 participants attended at five remote sites via the Access Grid. The hands-on tutorial session of the workshop was coordinated among local and remote participants using the Resource's BioCoRE collaboratory. Evaluations were again very high, and the event provided all of the institutions involved with valuable experience in remote training.

VMD: Visualization of Diverse Biomolecular Information

The growth of bioinformatics data in recent years has changed the face of biomolecular modeling. Structures must be examined in the context of their conserved sequences, relation to functionally similar proteins, and their role in the genome. Only a global view of sequence information can help with this. We have integrated a sequence viewer into VMD*, our molecular visualization and analysis tool. The sequence viewer is one of several major features added to VMD during the funding period.

The experimentally determined three-dimensional structure of a biomolecule is the necessary starting point for theoretical modeling approaches, from molecular dynamics simulations to quantum chemistry calculations. A biomolecule's structure provides information about its function, such as the shape of enzymatic transition states, molecule-molecule docking and recognition, as well as other mechanical and chemical properties. The sequence of a protein molecule provides complimentary information. An amino acid sequence both describes local chemical properties and places the protein in context with other known proteins via techniques such as database searches for conserved sequences.

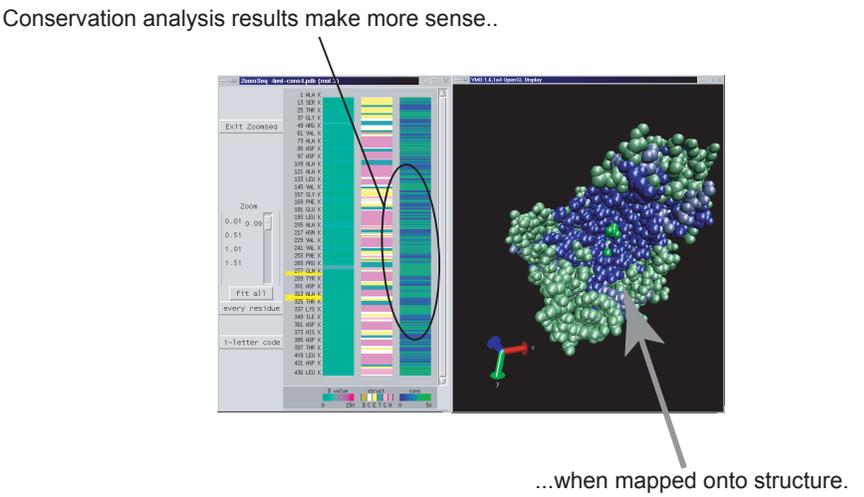

Figure 3: Any sequence-based information can be mapped onto the structure of a molecule, including results from conservation searches.

VMD can manage and display both sequence and structure data of a biomolecule, providing a number of convenient approaches to combine the two to characterize the biomolecule. The VMD Sequence window provides a global view of a protein's sequence, with multiple columns depicting different properties with colors. The Structure column provides secondary structure information, the B-value column can display temperature factors of structure determination, or can be customized to a value computed by the user.

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

The most important use of the Sequence window is connecting sequence-based analysis results to 3D structure. Any bioinformatic database or genomic analysis results can be loaded into the sequence viewer to be mapped onto 3D structure. An example of conservation analysis results mapped onto structure is presented in Figure 3. The 3D-Structure and Sequence windows are directly connected. Selecting a residue in the Sequence window will highlight the corresponding residue in the 3D structure; selecting a residue in the 3D structure will highlight a list entry in the Sequence listing.

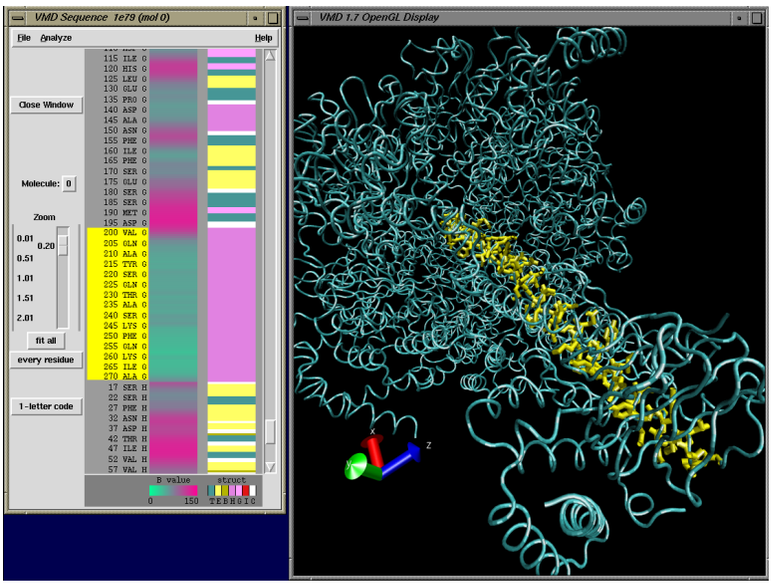

Figure 4: The Sequence window, zoomed out to display the entire protein sequence of ATP Synthase F_1, and highlighting a long helical stretch of the protein. The side-by-side comparison of properties makes it clear that the helical region also has a lower B-value than neighboring stretches of the protein.

The Sequence view can be zoomed out to display the entire sequence, showing properties across the whole molecule at once — this can be convenient when examining overall properties and browsing large sections of a protein with hundreds or thousands of residues, as shown in Figure 4. The view can be zoomed in to enumerate every residue of a protein, especially helpful when reading a journal article about an unfamiliar molecule, since proteins are routinely discussed by structural biologists with references to individual residue numbers. Motifs and other features are often referred to by their combined single-letter amino acid names, such as ATP synthase's "DELSEED" sequence, which are easily seen in the Sequence window when single-letter amino acid names are specified. The sequence window also allows basic sequence-structure exploration, such as checking periodicity of α-helix turns and hydrogen bond partners.

Many features remain to be added to expand sequence-structure analysis. Already prototyped are: better support for multiple-column data loading and comparison; residue vs. time property plots to identify events during trajectories. Other plans include distance matrix-style residue-residue plots and improved connections to external analysis tools.

BioCoRE: Biological Collaborative Research Environment

BioCoRE (*Bio*logical *Co*llaborative *R*esearch *E*nvironment)* is funded through an NIH supplemental award obtained in the Spring of 1999 to establish a testbed to facilitate collaborative work between biomedical researchers located at the same or geographically distant sites.

BioCoRE supports four basic types of activities: (1) utilizing a wide range of computational tools; (2) keeping records; (3) communicating with collaborators; and (4) writing multi-authored articles and reports. This functionality has been grouped into the following components of BioCoRE: Workbench, Notebook, Conferences, and Documents. A built-in evaluation component guarantees an ongoing assessment of BioCoRE development and the effectiveness of the new environment by monitoring and recording system usage for later analysis.

By using a standard web-browser (on a desktop or laptop computer or handheld PDA) scientists create projects and invite collaborators to join. All project data is secure and can be shared only by the specific project team. Researchers use BioCoRE to submit jobs to supercomputers or other remote sites, view molecules together across distances and easily create input files for supercomputer runs. BioCoRE features a synchronous and asynchronous chat, a project-wide "bookmarks" file that enables the sharing of web links as well as a web-based filesystem that is accessible to the BioCoRE project members. This filesystem is used to share files of interest and to simplify publication preparations via a seamless transport of document files among project members.

Due to its web-based nature, BioCoRE's release system is different from stand alone programs such as VMD or NAMD. Users accessing BioCoRE via their web browsers automatically receive the most recent version on the server. This allows the Resource to update BioCoRE frequently and to respond to bug reports in a timely manner.

Shortly after receiving the supplemental award to create BioCoRE, a test collaboratory server was setup at the Resource. This server has been used for testing and new feature development. Researchers have been encouraged to join the BioCoRE environment at the Resource.

This has worked well for the initial testing phase. However, hosting all researchers from around the world on a single server is a suboptimal long-term solution:

- Speed — Remote researchers accessing the Resource's collaboratory server experience network delays that they would not have if they were using a server local to their site.

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

- Security — Some researchers (particularly those in industry) have privacy concerns with hosting their scientific projects at external locations (such as the Resource).
- Limited Capacity — The Resource enjoys large, yet finite server assets. We have limited CPU power and disk space to devote to large numbers of researchers.

To address these issues, the Resource has released the server software to the research community. Researchers can access their collaboratory server as quickly as their internal network will allow, and they can control access to the machine as they desire. Researchers can feel safe knowing that the BioCoRE servers are running on their own local systems. Installation of multiple collaboratory servers also allows the Resource to share server capacity demands with outside groups.

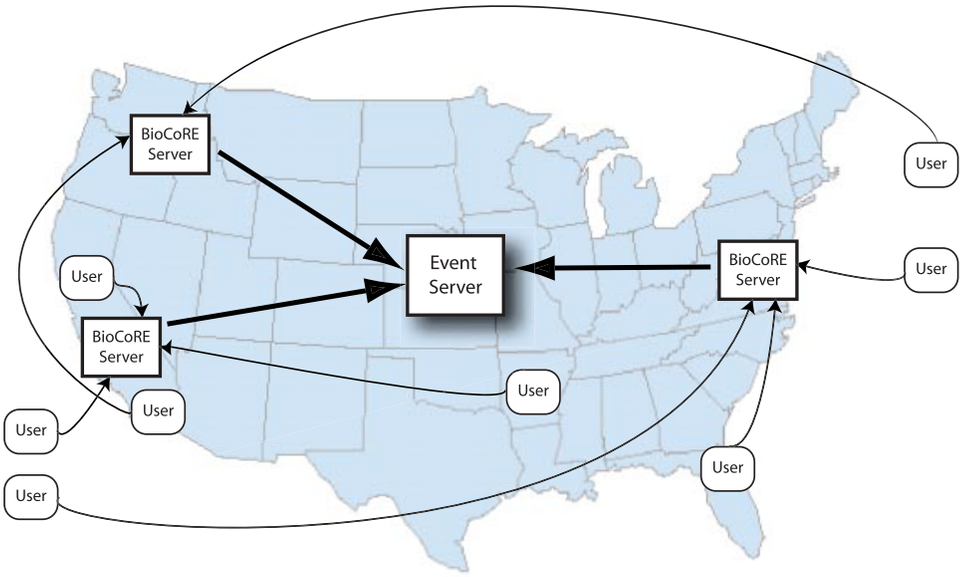

Figure 5: Connections between users, local BioCoRE servers, and the evaluation logging server

The Resource has exerted considerable effort to set up a separate evaluation logging server that resides at the Resource, accepts connections from the collaboratory servers at the various research groups that have installed them, and logs server usage data for further study (see Figure 5). With the release of server software, the additional challenge of collecting usage information for the evaluation component of the project has arisen.

Mechanobiology

Many proteins experience mechanical forces in vivo. Two examples of these so-called mechanical proteins are the muscle protein titin and the extracellular matrix protein fibronectin. Titin is responsible for providing passive elasticity and extensibility for muscle under tension [21,22]. The elasticity of titin is partially due to its ∼100 immunoglobulin-like (Ig) modules in the titin I-band [23]. Fibronectin is primarily composed of ∼20 homologous modules (classified as fibronectin repeats FN-I, FN-II, and FN-III) that are structurally similar to Ig modules built in β-sandwich motif. Cells assemble fibronectins into fibrillar networks that are essential in transmitting signals between cells for regulating cell migration, proliferation and differentiation [24]. The fibrillar networks couple cells mechanically to their environment and to neighboring cells, providing a substrate for anchorage and guiding cell migration during embryonic development and wound healing.

To fulfill their physiological roles, Ig domains and FN-III are thought to unfold upon external stress. Reversible unfolding of Ig repeats [25] and FN-III modules [26] has been demonstrated with atomic force microscopy (AFM), and later extended in a series of ground-breaking publications [27–32]. Although AFM has provided valuable information about the forces required for the sequential rupture of protein modules, the method are not well suited to constructing an atomic picture of the unfolding pathway due to the limited resolution. Structural insights into the mechanical unfolding pathways are crucial for determining how the functional states of proteins are regulated by external force. To complement the AFM observations, steered molecular dynamics (SMD) simulations have been conducted with Ig domain I27* [29, 33–37] and FN-III$_{7-10}$ modules† [38–40] (reviewed in [11, 41, 42]). This series of papers constitute one of the Resource's main scientific successes during the past funding period.

SMD simulations of I27 demonstrated that the two steps of unfolding indicated in AFM experiments correspond to two sequential events of inter-strand hydrogen bond rupture (see Figure 6). The two sets of hydrogen bonds are the three hydrogen bonds connecting β-strands A and B of I27, and the six bridging between β-strands A' and G. The first set of hydrogen bonds ruptures at weak forces above 50 pN near the N-terminus of the domain (see Figure 6**b**), causing an intermediate observed as a "hump" in force-extension profiles from AFM experiments (see Figure 6**d**). Site-directed mutagenesis experiments that disrupted the predicted hydrogen bonds were suggested to collaborating AFM experimentalists. Indeed, the mutation eliminated the forced-unfolding intermediate in AFM observations [29] (see Figure 6**e**). The second set of hydrogen bonds breaks at stronger forces of 150 to 300 pN, initiating complete unfolding.

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

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

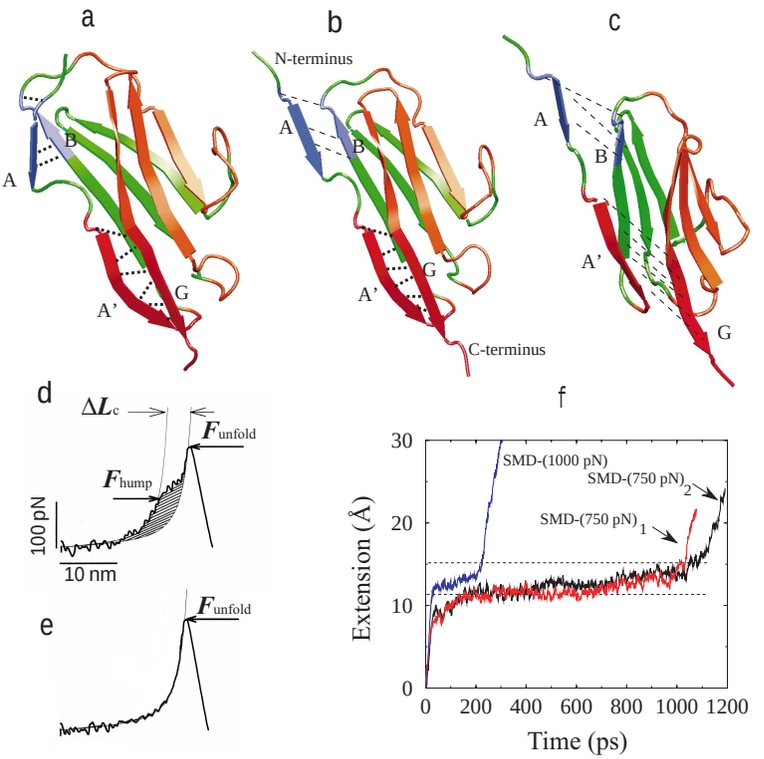

Figure 6: Forced unfolding of titin immunoglobulin module I27 by SMD simulations and AFM experiments. **(a-c)** Representative snapshots of the three-phase unfolding scenario of I27 observed in SMD simulations [36]. **(d-e)** The first peak in the force-extension curve for I27 octamer (d) and for the Lys 6 → Pro 6 mutant (e) from AFM experiments (adapted from [29].) **(f)** Extension profiles from SMD simulations for constant force protocols.

Quantitative agreement was also found in the height of the kinetic barrier that has been probed in both AFM experiments [43] and SMD simulations [35]. Moreover, the scenarios of unfolding provided by SMD simulations revealed the important roles of water molecules in the unfolding of the protein: during barrier crossing water molecules were found to attack inter-strand hydrogen bonds, assisting the unfolding of I27 domains [36]. The competition for hydrogen bond partners with water molecules is also important for the backbone oxygen and hydrogen atoms to reform hydrogen bonds in the spontaneous refolding process of I27. By driving water molecules away and reforming six A'-G backbone hydrogen bonds, a partially refolded I27 has been observed after release of external forces [37].

Our recent SMD simulations of the titin I1 domain, the first known structure [44] from the proximal Ig region of the titin I band, have revealed that I1 has different mechanical response from I27 because of its different mechanical design. First, the mechanical stability of I1 domains is slightly weaker than that of I27. The main reason is that I1 domains have no more than four concurrently breaking backbone hydrogen bonds, which contribute to the force peaks recorded in simulations; by contrast, I27 has six A'-G backbone hydrogen bonds that break simultaneously [33]. Second, the mechanical stability

of I1 is largely due to the six backbone hydrogen bonds between its A- and B-strands. Third, I27 exhibits an ∼6 Å extension 'hump' revealed in force-extension curves [29]; I1 domains, however, should not exhibit such hump at forces below 200 pN due to the large number of A-B inter-strand hydrogen bonds. The fourth difference between I1 and I27 stems from a disulfide bond in I1. Our simulations of oxidized and reduced I1 revealed that the disulfide bridge between Cys^{36} and Cys^{31} increases the mechanical stability and limits the extension of I1 to 220 Å.

The same SMD protocols have also been applied to unfold FN-III_{7-10} modules. FN-III_{10} mediates cell adhesion to surfaces via its integrin binding motif [45], Arg-Gly-Asp (RGD), that is located at the apex of the loop connecting β-strands F and G. By separating the G-strand from the remaining fold, the distance between the apex of the RGD-containing loop and the module surface was shortened. This conformational change reduces the affinity to integrin. The RGD loop thus constitutes a mechanosensitive switch for recognition by integrin receptors [38]. Systematic constant force SMD simulations have been conducted with fibronectin monomers FN-III_{7-10}. Two distinct kinetic barriers have been identified for short stretches of less than 60 Å [39].

To probe unfolding intermediates of FN-III_{10} at extension longer than 60 Å, the proteins have been stretched to their full extension in water boxes of 126,000 atoms. FN-III_{10} was found to exhibit three distinct unfolding pathways. In one of the pathways a meta-stable intermediate found at extension 100 Å may serve as a basis for fibronectin self-assembly through a proposed β-strand swapping mechanism [46]. Water box models were also used to extend a FN-III_{9-10} dimer [40]. These simulations identified an intermediate in which the length of the linker chain between the two modules is increased by 17 Å, a change that could switch off the signaling between FN modules and transmembrane protein integrins.

Completed Collaborations

During the past funding period, many exciting collaborations were completed. These projects made use of the expertise of the staff and the researchers at the Resource as well as of the Resource's unique modeling tools and computational laboratory. The Resource receives many requests for collaborations and selects projects on the basis of quality and biomedical relevance. Below are listed some of the completed projects that will not be continued during the next funding period. Much further collaborative work has been accomplished [29,38,39,47,48]. The first eight projects focus on biomedical science ranging from the development of high pressure gel mobility shift analysis to a study of lipoproteins. Three other projects advance the computational research of the Resource and involve computer scientists, computational biologists, and electrical engineers. The accomplishments of the ongoing collaborations will be described separately in the following sections.

1. Dissecting the molecular origins of protein-nucleic acid recognition: High pressure and molecular dynamics

T. W. Lynch, D. Kosztin, M. A. McLean, K. Schulten, and S. G. Sligar

Biophysical Journal, 82:93-98, 2002

The fundamental processes by which proteins recognize and bind to nucleic acids are critical to understanding cellular function. To explore the factors involved in protein-DNA recognition, we used hydrostatic pressure to perturb the binding of the BamHI endonuclease to cognate DNA, both in experiment and in molecular dynamic simulations. A new technique of high pressure gel mobility shift analysis was employed to test the effects of elevated hydrostatic pressure on the binding of BamHI to its cognate recognition sequence. Upon application of a pressure of 500 bar, the equilibrium dissociation constant binding to the cognate site was found to increase nearly 10-fold. A challenge has been to link this type of pure thermodynamic measurement to functional events occurring at the molecular level. Thus, we used molecular dynamic simulations at both ambient and elevated pressures to reveal details of the direct and water-mediated interactions between BamHI and cognate DNA, which allow explanation of the effects of pressure on site-specific protein-DNA binding and complex stability.

2. Steered molecular dynamics simulation of the Rieske subunit motion in the cytochrome bc_1 complex

S. Izrailev, A. R. Crofts, E. A. Berry, and K. Schulten
Biophysical Journal, 77:1753-1768, 1999

Crystallographic structures of the mitochondrial ubiquinol/cytochrome c oxidoreductase (cytochrome bc_1) complex involves a substantial movement of the soluble head of the Rieske iron-sulfur protein (ISP) between reaction domains in cytochrome b and cytochrome c_1 subunits. In this paper we report the results of steered molecular dynamics simulations inducing, through an applied torque within 1 ns, a 56° rotation of the soluble domain of ISP. For this purpose, a solvated structure of the bc_1 complex in a phospholipid bilayer (a total of 206,720 atoms) was constructed.* A subset of 91,061 atoms was actually simulated with 45,131 moving atoms. Point charge distributions for the force field parameterization of heme groups and the Fe_2S_2 cluster of the Rieske protein included in the simulated complex were determined. The simulations showed that rotation of the soluble domain of ISP is actually feasible. Several metastable conformations of the ISP during its rotation were identified and the interactions stabilizing the initial, final and intermediate positions of the soluble head of the ISP domain were characterized. A pathway for proton conduction from the Q_o site to the solvent has been identified.

3. Predicting the structure of apolipoprotein A-I in reconstituted high density lipoprotein disks

J. C. Phillips, W. Wriggers, Z. Li, A. Jonas, and K. Schulten
Biophysical Journal, 73:2337-2346, 1997

In reconstituted high density lipoproteins, apolipoprotein A-I and phosphatydylcholines combine to form disks in which the amphipathic α-helices of apolipoprotein A-I bind to the edge of a lipid bilayer core, shielding the hydrophic lipid tails from the aqueous environment. We have employed experimental data, sequence analysis, and molecular modeling to construct an atomic model of such a reconstituted high density lipoproteins disk consisting of two apolipoprotein A-I proteins and 160 palmitoyloleoyl-phosphatidylcholine lipids.† The initial globular domain (1-47) of apolipoprotein A-I was excluded from the model, which was hydrated with an 8-$\AA$ shell of water molecules. Molecular dynamics and simulated annealing were used to test the stability of the model. Both head-to-tail and head-to-head forms of reconstituted high density lipoproteins were simulated. In our simulations the protein contained and adhered to the lipid bilayer while providing good

*URL: `http://www.ks.uiuc.edu/Research/smd_imd/bc1/`

†URL: `http://www.ks.uiuc.edu/Research/apoa1/`

coverage of the lipid tails.

4. Structure prediction of a complex between the chromosomal protein HMG-D and DNA

A. Balaeff, M. E. A. Churchill, and K. Schulten

PROTEINS: Structure, Function, and Genetics, 30:113-135, 1998.

Non-histone chromosomal proteins are an important part of nuclear structure and function due to their ability to interact with DNA to form and modulate chromatin structure and regulate gene expression. However, the understanding of the function of chromosomal proteins at the molecular level has been hampered by the lack of structures of chromosomal protein-DNA complexes. We have carried out a molecular dynamics modeling study to provide insight into the mode of DNA binding to the chromosomal HMG-domain protein, HMG-D.[‡] Three models of a complex of HMG-D bound to DNA were derived through docking the protein to two different DNA fragments of known structure. Molecular dynamics simulations of the complexes provided data indicating the most favorable model. This model was further refined by molecular dynamics simulation and extensively analyzed. The structure of the corresponding HMG-D-DNA complex exhibits many features seen in the NMR structures of the sequence-specific HMG-domain-DNA complexes, lymphoid enhancer factor 1 (LEF-1) and testis determining factor (SRY). The model reveals differences from these known structures that suggest how chromosomal proteins bind to many different DNA sequences with comparable affinity.

5. Probing the role of structural water in a duplex oligodeoxyribonucleotide containing a water-mimicking base analogue

D. Kosztin, R. Gumport, and K. Schulten

Nucleic Acids Research, 27:3550-3556, 1999

Molecular dynamics simulations were performed on models of the dodecamer DNA double-stranded segment, $[\mathrm{d(CGCGAATTCGCG)}]_2$, in which each of the adenine residues, individually or jointly, was replaced by the water-mimicking analogue 2'-deoxy-7-(hydroxymethyl)-7-deazaadenosine ($\mathrm{hm^7c^7dA}$).[§] The simulations, when compared to those of the dodecamer itself, show that incorporation of the analogue affects neither the overall DNA

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

[§]URL: `http://www.ks.uiuc.edu/Research/pro_DNA/dna_w_analog/`

structure nor its hydrogen-bonding and stacking interactions when a single individual base is replaced by the analog. Furthermore, the water molecules near the bases in the singly-substituted oligonucleotides are similarly unaffected. Double substitutions lead to differences in all the aforementioned parameters with respect to the reference sequence. The results suggest that the analogue provides a good mimic of specific "ordered" water molecules observed in contact with DNA itself and at the interface between protein and DNA in specific complexes.

6. Structure and dynamics of calmodulin in solution

W. Wriggers, E. Mehler, F. Pitici, H. Weinstein, and K. Schulten
Biophysical Journal, 74:1622-1639, 1998

To characterize the dynamic behavior of calmodulin in solution, we have carried out molecular dynamics simulations of the Ca^{2+}-loaded structure. The crystal structure of calmodulin was placed in a solvent sphere of radius 44 $\AA$, and 6 Cl^- and 22 Na^+ ions were included to neutralize the system and to model a 150 mM salt concentration. The total number of atoms was 32,867. During the 3 ns simulation the structure exhibits large conformational changes on the nanosecond time scale. The central alpha-helix, which has been shown to unwind locally upon binding of calmodulin to target proteins, bends and unwinds near residue Arg74. We interpret this result as a preparative step in the more extensive structural transition observed in the "flexible linker" region 74-82 of the central helix upon complex formation. The major structural change is a reorientation of the two Ca^{2+}-binding domains with respect to each other and a rearrangement of alpha-helices in the N-terminus domain which make the hydrophobic target peptide binding site more accessible. This structural rearrangement brings the domains to a more favorable position for target binding, poised to achieve the orientation observed in the complex of calmodulin with myosin-light-chain-kinase. Analysis of solvent structure reveals an inhomogeneity in the mobility of water in the vicinity of the protein which is attributable to the hydrophobic effect exerted by calmodulin's binding sites for target peptides.

7. Efficient light harvesting through carotenoids

T. Ritz, A. Damjanovic, K. Schulten, J. Zhang, and Y. Koyama
Photosynthesis Research, 66:125-144, 2000

We investigate the factors that control the efficiency of carotenoid-chlorophyll excitation

transfer in photosynthetic light harvesting.[¶] We review the recently developed theory that describes electronic couplings between carotenoids and chlorophylls and we investigate in particular the influence of length of conjugated system and of symmetry breaking on the couplings, focussing on the structurally solved lycopene-BChl system of LH2 from *Rhodospirillum molischianum* and the peridinin-Chla system of PCP from *Amphidinium carterae*. In addition, we review recent spectroscopic data for neurosporene, spheroidene, and lycopene, three carotenoids with different lengths of conjugated systems. On the basis of the measured energies, emission lineshapes, solution and protein environment lifetimes for their $2A_g^-$ and $1B_u^+$ states as well as of the theoretically determined couplings, we conclude that the transfer efficiencies from the $2A_g^-$ state are controlled by the Car($2A_g^-$)-BChl(Q_y) electronic couplings and the $2A_g^- \rightarrow 1A_g^-$ internal conversion rates. We suggest that symmetry breaking rather than length of conjugated system dominate couplings involving the $2A_g^-$ state. Differences in transfer efficiencies from the $1B_u^+$ state in LH2 and PCP are found to be dominated by the differences in spectral overlap. The role of the $1B_u^+$ state is likely to be influenced by a lower-lying (in longer polyenes), optically forbidden $1B_u^-$ state.

8. Self-organizing neural networks bridge the biomolecular resolution gap
W. Wriggers, R. A. Milligan, K. Schulten, and J. A. McCammon
Journal of Molecular Biology, 284:1247-1254, 1998

Topology representing neural networks are employed to generate pseudo-atomic structures of large-scale protein assemblies by combining high-resolution data with volumetric data at lower resolution. As an application example, actin monomers and structural subdomains are located in a 3D image reconstruction from electron micrographs. To test the reliability of the method, the resolution of the atomic model of an actin polymer is lowered to a level typically encountered in electron microscopic reconstructions. The atomic model is restored with a precision nine times the nominal resolution of the corresponding low-resolution density. The presented self-organizing computing method may be used as an information processing tool for the synthesis of structural data from a variety of biophysical sources.

9. Algorithmic challenges in computational molecular biophysics
T. Schlick, R. Skeel, A. Brünger, L. Kalé, J. A. Board Jr., J. Hermans, and K. Schulten
Journal of Computational Physics, 151:9-48, 1999

[¶]URL: `http://www.ks.uiuc.edu/Research/bio_ener/LH_2/`

A perspective of biomolecular simulations today is given, with illustrative applications and an emphasis on algorithmic challenges, as reflected by the work of a multidisciplinary team of investigators from five institutions. Included are overviews and recent descriptions of algorithmic work in long-time integration for molecular dynamics, fast electrostatic evaluations, crystallographic refinement approaches, and implementation of large, computer-intensive programs on modern architectures.

10. A visual computing environment for very large scale biomolecular modeling

M. Zeller, J. C. Phillips, A. Dalke, W. Humphrey, K. Schulten, R. Sharma, T. S. Huang, V. I. Pavlovic, Y. Zhao, Z. Lo, and S. Chu

Proceedings of the 1997 IEEE International Conference on Application-specific Systems, Architectures and Processors (ASAP), pages 3-12. IEEE Computer Society Press, 1997

Knowledge of the complex molecular structures of living cells is being accumulated at a tremendous rate. Key technologies enabling this success have been high performance computing and powerful molecular graphics applications, but the technology is beginning to seriously lag behind challenges posed by the size and number of new structures and by the emerging opportunities in drug design and genetic engineering. A visual computing environment is being developed which permits interactive modeling of biopolymers by linking a 3D molecular graphics program with an efficient molecular dynamics simulation program executed on remote high-performance parallel computers. The system will be ideally suited for distributed computing environments, by utilizing both local 3D graphics facilities and the peak capacity of high-performance computers for the purpose of interactive biomolecular modeling. To create an interactive 3D environment three input methods will be explored:
(1) a six degree of freedom "mouse" for controlling the space shared by the model and the user; (2) voice commands monitored through a microphone and recognized by a speech recognition interface; (3) hand gestures, detected through cameras and interpreted using computer vision techniques. Controlling 3D graphics connected to real time simulations and the use of voice with suitable language semantics, as well as hand gestures, promise great benefits for many types of problem solving environments. Our focus on structural biology takes advantage of existing sophisticated software, provides concrete objectives, defines a well-posed domain of tasks and offers a well-developed vocabulary for spoken communication.

11. Speech/gesture interface to a visual-computing environment

R. Sharma, M. Zeller, V. I. Pavlovic, T. S. Huang, Z. Lo, S. Chu, Y. Zhao, J. C. Phillips, and K. Schulten

IEEE Computer Graphics and Applications, 20:29-37, 2000

Recent progress in 3D immersive display and virtual reality (VR) technologies has made possible many exciting applications. To fully exploit this potential requires "natural" interfaces that allow manipulating such displays without cumbersome attachments. In this article we describe using visual hand-gesture analysis and speech recognition for developing a speech/gesture interface to control a 3D display. The interface enhances an existing application, VMD, which is a VR visual computing environment for structural biology. The free-hand gestures manipulate the 3D graphical display, together with a set of speech commands.

BTA UNIT: C

TITLE: Aquaporins

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

AXIS I: 2

AXIS II: 74h,89

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% BRTP $: 5%

ABSTRACT: Aquaporins (AQPs)* are a family of membrane channel proteins abundantly present in all life forms [1]. They facilitate passive but efficient permeation of water and small solutes such as glycerol [2] across the membrane, but completely exclude charged species, such as protons. Impaired function of AQPs are related to diseases such as *diabetes insipidus* [1]. The structures of two AQPs, the human aquaporin-1 (AQP1) and the E. coli glycerol uptake facilitator (GlpF), have been determined [5, 7, 49].

The Resource has performed MD simulations of AQP1 and GlpF embedded in fully hydrated lipid bilayers, revealing the formation of single files of water inside the channels [9, 10], and the critical role of the two highly conserved motifs (the NPA motifs) in the function of the channels. The simulations were performed in constant pressure and temperature (NpT), calculating full electrostatic interactions with the program NAMD2 [16] on systems of about 100,000 atoms. The conduction pathway, being fully described in the simulations, was found to be intimately correlated with the conserved secondary structure of the two loops in the protein [10]. Moreover, the conduction event is facilitated by a lubricating effect of water inside the channel [10].

The Resource's steered molecular dynamics (SMD) simulations have revealed binding sites for the substrate as well as the barriers against its movement inside the channel, and provided for the first time both quantitative and qualitative insight into the aquaporin facilitated permeation of metabolic substrates across cell membranes [12].

We have also developed a method to induce a hydrostatic pressure difference across the membrane in MD simulations which can be used to measure the osmotic permeability of water channels, a physicochemical property that can be directly measured experimentally [15]. Detailed analysis of the dynamics of water inside the channel provides a mechanism precluding proton transport in AQPs. The simulations showed that the arrangement of water molecules in the channel is highly unfavorable for proton transfer [14].

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

BTA UNIT: T, D

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

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% BRTP $: 13%

ABSTRACT: NAMD is a parallel, object-oriented molecular dynamics code designed for high performance simulation of large biomolecular systems [16]. NAMD employs the prioritized message-driven execution capabilities of the Charm++/Converse parallel runtime system,* allowing excellent parallel scaling on both massively parallel supercomputers and commodity workstation clusters.

NAMD parallel scalability has grown by two orders of magnitude during the grant period, from 8–16 processors in 1997 to 512–1024 processors today. Furthermore, today's processors themselves are a factor of four faster than those available in 1997, the NAMD source code is more efficient, and the modern simulation runs with particle mesh Ewald full electrostatics.

*URL: `http://charm.cs.uiuc.edu/`

NAMD now provides a wide range of simulation methods, including constant pressure and temperature dynamics, conformational and alchemical free energy perturbation, and a variety of steering methods. In particular, a simulation may be steered interactively via a network connection to VMD and a haptic interface device. NAMD incorporates the Tcl scripting language, which allows the user to implement new simulation protocols without recompiling.

NAMD was originally designed to complement the capabilities of the modeling program X-PLOR by providing an efficient, parallel simulation engine. The initial X-PLOR file compatibility has been extended to include CHARMM, AMBER, and GROMACS. In response to user demand for an alternative to these existing packages, the psfgen utility for generating NAMD input files has been created and incorporated into VMD, providing a complete modeling toolkit.

NAMD has had eight major public releases, starting with version 1.3 in July 1995 and continuing through versions 1.4, 1.5, 2.0, 2.1, 2.2, and 2.3 to the most recent, 2.4, released in March 2002. NAMD is distributed free of charge via the web[†] as both source code and convenient precompiled binaries for eleven platforms, including Microsoft Windows and Mac OS X. NAMD has over 3600 registered users, over 500 of whom are NIH-funded.

Two NAMD workshops have been presented, the first in August 2001 to 22 participants at the Pittsburgh Supercomputing Center, and the second in April 2002 to 32 local participants at the National Center for Supercomputing Applications and to an additional 61 remote participants via the Access Grid.

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

BTA UNIT: T, D

TITLE: VMD: High Performance, Low Cost Molecular Visualization

KEYWORDS: molecular visualization, interactive simulation

AXIS I: 9

AXIS II: 42, 89

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% BRTP $: 13%

ABSTRACT: VMD [50] is an advanced 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 tasks.* VMD runs on all major operating systems and supports computers ranging from laptops to graphics supercomputers, allowing it to scale with 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.

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

VMD developments in the last year have expanded the range of data it can display, and analyze. VMD includes a new tool for browsing sequence data and highlighting sequence selections in the displayed 3-D structure. A new Ramachandran angle plotting tool provides researchers with the unique ability to animate angle plots over the course of a molecular dynamics trajectory. New volumetric rendering features have been added for the display of electron density maps, electron orbitals, potential maps, and user-defined data sets.

The "psfgen" structure building system was adapted as a plugin so that structure building can now be performed within VMD. New web-based control and structure building features in VMD were heavily used during a hands-on workshop held at NCSA in April 2002. An easy-to-use movie generation plugin automates all of the tasks involved in producing movies of biomolecular structures and molecular dynamics trajectories, allowing inexperienced VMD users to take advantage of its most powerful animation and rendering features.

Three major VMD updates have been released in the past year, with more than 3,924 unique users of the most mature release. VMD is available free of charge in both binary and source code forms, and is distributed via the web. Nine major versions of VMD have been publically released since 1997. More than 18,500 unique users have registered and downloaded VMD since January 7, 2000. Over 3,100 of these users are NIH funded researchers.

BTA UNIT: T, C, D

TITLE: BioCoRE: Biological Collaborative Research Environment

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

AXIS I: 9

AXIS II: 42,51, 89

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% BRTP $: 18%

ABSTRACT: BioCoRE [51] is a freely available web-based collaborative environment designed to enhance the biomedical research process and promote training. By using a standard web-browser (on a desktop or laptop computer or handheld PDA) scientists create projects and invite collaborators to join. All project data is secure and can be shared only within the specific project team. Researchers use BioCoRE to submit jobs to supercomputers or other remote sites, view molecules together across distances and easily create input files for supercomputer runs. BioCoRE features a synchronous and asynchronous chat, a project-wide "bookmarks" file that enables the sharing of web links as well as a web-based filesystem that is accessible to the BioCoRE project members. This filesystem is used to share files of interest and to simplify publication preparations via a seamless transport of document files among project members. Summary pages within BioCoRE regularly inform the project team of the project status, including individual tasks of each team member. BioCoRE sessions are automatically recorded and can be reviewed later by the project leader and the other team members.*

Major BioCoRE developments in the past year include the ability to use Globus for job submission. This allows easy access to all Alliance supercomputers. BioCoRE now contains a web-based file repository that collaborators can use to share important files. In the Spring of 2002, the Resource completed work necessary to allow research groups the ability to download and install their own BioCoRE collaborative servers.

The Resource has been active in dissemination of BioCoRE. In the past year, an SCGlobal Access Grid presentation was given at the SC 2001 conference, which was viewed by participants from around the world. BioCoRE posters were well-received at the Biophysical Society 2002 meeting and the 2002 Alliance All-Hands meeting. BioCoRE was also used for the hands-on portion of the NAMD workshops at PSC in August 2001 and NCSA in April 2002.

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

BTA UNIT: C

TITLE: Mechanobiology

KEYWORDS: titin, fibronectin, protein unfolding, immunoglobulin, atomic force microscopy

AXIS I: 13,20

AXIS II: 74h

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% BRTP $: 2.5%

ABSTRACT: Many proteins experience mechanical forces in vivo. Two examples of these so-called mechanical proteins are the muscle protein titin and the extracellular matrix protein fibronectin. Reversible unfolding of Ig repeats [25] and FN-III modules [26] has been demonstrated with atomic force microscopy (AFM). Although AFM has provided valuable information about the forces required for the sequential rupture of protein modules, the method are not well suited to constructing an atomic picture of the unfolding pathway. To complement the AFM observations, steered molecular dynamics (SMD) simulations have been conducted with Ig domain I27 [29, 33–37] and FN-III$_{7-10}$ modules [38–40] (reviewed in [11, 41, 42]).

SMD simulations demonstrated that I27 unfolds in two steps, corresponding to two sequential events of inter-strand hydrogen bond rupture [29, 33, 35]. Quantitative agreement was also found in the height of the kinetic barrier probed [35]. Moreover, the scenarios of unfolding provided by SMD simulations revealed that during barrier crossing water molecules attack inter-strand hydrogen bonds, assisting the unfolding of I27 domains [36]. By driving water molecules away and reforming six A'-G backbone hydrogen bonds, a partially refolded I27 has been observed after release of external forces [37]. Our recent SMD simulations of the titin I1 domain have found that I1 has different mechanical response from I27 due to their different inter-strand hydrogen bonding structures.

SMD protocols have also been applied to unfold FN-III$_{7-10}$ modules. Simulations of FN-III$_{10}$ suggest that the conformational changes of the so-called RGD loop constitutes a mechanosensitive switch for recognition by integrin receptors [38]. Systematic constant force SMD simulations of FN-III$_{7-10}$ revealed two distinct kinetic barriers that are common to all four FN-III modules [39]. To probe unfolding intermediates of FN-III$_{10}$ at extension longer than 60 Å, the proteins have been stretched to their full extension in water boxes of 126,000 atoms. A meta-stable intermediate found at extension 100 Å may serve as a basis for fibronectin self-assembly through proposed β-strand swapping [46]. Water box models were also used to extend a FN-III$_{9-10}$ dimer [40]. These simulations identified an intermediate in which the length of the linker chain between the two modules is increased by 17 Å, a change that could switch off the signaling between FN modules and transmembrane protein integrins.

BTA UNIT: T, D

TITLE: Interactive Molecular Dynamics

KEYWORDS: molecular dynamics, molecular visualization, haptic feedback

AXIS I: 9

AXIS II: 42, 89

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% BRTP $: 4%

ABSTRACT: *Interactive Molecular Dynamics** (IMD) allows biomedical researchers to manipulate simulated molecules in real time, to gain intuition about the systems they are studying. IMD has been developed by the resource [52], building on earlier work [53] to combine VMD [50] and NAMD [16]. Researchers can use the system with several different virtual-reality devices, including a three-dimensional force-feedback device that allows them to feel the forces they exert as they manipulate the simulated molecules. IMD is supported by VMD and NAMD, available on the Resource website, and can be used on a variety of computer platforms. IMD can also be used with simulation and visualization programs besides NAMD and VMD; one application connects VMD to the molecular dynamics software ProtoMol [54]. Our implementation of IMD is related to an earlier system involving VMD, designed by others [55].

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

Interactive Molecular Dynamics was used successfully to examine the passage of sugar through the glycerol channel GlpF. Real-time interaction allowed researchers to experiment with different conformations of the sugar molecules in each part of the channel and predict their conduction pathways. The study verified the mechanism of selectivity in the system that was originally proposed [7] and showed that the important dipole reversal observed in water [14] is also present in much larger sugar molecules. A publication describing the results is currently in preparation.

A new application of Interactive Molecular Dynamics that is being developed by the Resource simplifies the process of constructing molecular dynamics simulations. To construct a new simulation, researchers typically have to bring proteins, lipids, and various substrates into physical contact, which requires careful positioning. With interactive molecular dynamics, researchers can start a small simulation of the pieces that need to be aligned (using the *molten zone* method [55]), then push them by hand into the desired positions. This method is particularly useful when the pieces need to be bent to fit together — it has been used in several projects at the Resource for this reason. The script that makes this possible will be available soon from the VMD website.

BTA UNIT: T, D

TITLE: JMV: Java Molecular Viewer

KEYWORDS: molecular visualization, Java-based shared molecular viewer, Java3D, web tools, interactive graphics

AXIS I: 9

AXIS II: 42, 89

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% BRTP $: 4%

ABSTRACT: JMV is a component-based molecular visualization program for web-based downloading and displaying of biomolecules, with collaboration features.* JMV is designed to function in several different modes of usage: as a standalone application, as an applet within a web browser, or as a molecular visualization component within other software.

JMV is written in the Java language, using Java3D for its graphics and 3-D rendering acceleration. Since Java and Java3D are platform independent technologies,

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

the same JMV binary will run on any platform supporting Java and Java3D. JMV benefits from the use of the rich set of programming interfaces provided by Java, particularly in its support for network file access and the extensibility of many common Java components. JMV also uses Java Beans, Java's component based architecture, which provides modularity and lets developers determine which of JMV's features they wish to display and their layout.

JMV borrows several key features and design idioms from VMD [50], our molecular visualization tool for large-scale biomolecules. JMV provides space filling molecular representations such as CPK, Licorice, Van der Waals spheres, as well as "lines", "bonds", and "tube" representations. JMV also supports stereoscopic display, and includes user-controllable lighting.

JMV is uniquely suited for web-based presentation and dissemination of molecules since it can be downloaded and run on-the-fly on computers with Java and Java3D support. Molecules can be loaded from BioCoRE's [51] shared filesystem, local and remote filesystems, and can be directly retrieved from the Protein Data Bank using a structure's 4 character PDB accession code.

BTA UNIT: T, C, D

TITLE: Algorithm Development

KEYWORDS: molecular dynamics, fast electrostatic methods, hierarchical interpolation, integration methods, Hamiltonian systems, symplectic integrators, multiple time stepping, stability, Langevin dynamics, software modularity

AXIS I: 9

AXIS II: 42, 48

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% BRTP $: 3%

ABSTRACT: The calculation of electrostatic forces dominates the computational work for molecular dynamics* (MD), even when fast electrostatic methods are employed. The multiple grid method [56], based on the hierarchical interpolation of softened pairwise potentials, has been developed as an alternative to existing fast methods. Stable dynamics for nonperiodic systems has been shown with a factor of four speedup over the fast multipole algorithm [57] as implemented by DPMTA [58], available in NAMD. Very limited testing with periodic systems has shown the multiple grid method to be competitive with the NAMD implementation of the particle-mesh-Ewald method [59] at lower accuracies, and further improvements in accuracy are expected through the use of higher order interpolation.

The trajectory computed by a symplectic integrator, such as Verlet [60] or Verlet-I/r-RESPA [61, 62], is very close to the exact trajectory of a "shadow" Hamiltonian [63]. A cheap and simple method for computing high order approximations to the shadow Hamiltonian has been discovered and applied to MD [64], providing a useful tool for monitoring accuracy during a simulation. It should also be possible to use the shadow Hamiltonian to modify forces to compensate for finite time step

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

errors, thus permitting longer step sizes, up to the stability limit, for almost all interactions.

Nonlinear stability limitations have recently been predicted and observed for multiple time stepping [65]. These restrict the longest time step used by the Verlet-I/r-RESPA integrator to less than 1/3 the period of the fastest normal mode, which for molecular dynamics is about 3.3 fs. More aggressive time stepping is possible with mild Langevin coupling [66,67], and its combination with the mollified impulse method [68,69] permits step sizes 3.5 times larger than Verlet-I/r-RESPA while still computing dynamic properties accurately.

The modularity of MD software has been improved through the creation of the MDAPI[†] (MD application programming interface). The MDAPI separates the force and integration calculations from the control and data management tasks, allowing a front end to efficiently drive an optimized MD engine. Plans are underway to include the MDAPI into the third generation of NAMD, which will improve the maintainability of NAMD and could eventually lead to the integration of VMD and NAMD into a single application framework.

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

BTA UNIT: C,T

TITLE: MscL Gating Mechanisms in *M. Tuberculosis* and *E. Coli*

KEYWORDS: mechanosensitive channel, molecular dynamics, surface tension, MscL, membrane protein

AXIS I: 2,7a

AXIS II: 74f,h; 77

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% BRTP $: 2.5%

ABSTRACT: Mechanosensitive (MS) channels * are integral membrane proteins that are gated by mechanical stresses in the membrane. MS channels play an important physiological role in living cells of diverse phylogenetic origins. In eukaryotes, MS channels play a role in important biological functions such as hearing, touch, and cardiovascular regulation [70], and are thought to mediate the stimulation of exocytosis by mechanical strain [71, 72]. A crystal structure of MscL from *M. tuberculosis* (Tb-MscL) [73] shows the structure of the channel in its closed form, leaving the structure of the open channel and the gating pathway unresolved. In the model proposed by our collaborators, the channel possesses two gates, one controlled by the constriction of the transmembrane helices, and the other composed of residues which are not resolved in the current MscL crystal structure. Though the model accounts for much of the patch clamp and mutagenesis data, many questions remain unanswered [74–76].

The Resource conducted simulations of Tb-MscL to determine what protein-lipid and intra-protein interactions are invoked during the response of the system to a mechanical stress. Such simulations necessarily require a complete description of the protein, lipid, and water environments. The large C-terminal domains, which extend into the cytoplasm, were omitted as mutant channels lacking this domain show no loss of activity [77]. Our initial simulations focused on the equilibrium properties of the closed MscL channel surrounded by a POPC bilayer; the solvated system contained 55,666 atoms [78].

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

Resource researchers performed applied surface tension simulations of Tb-MscL with no solvent or lipid [78] and obtained remarkably consistent results: the protein retained its secondary structure while significantly re-forming its tertiary structure to form a large pore. Retention of secondary structure was an important consistency check since the native lipid environment would not have allowed alternative hydrogen bonds to form. The observation that the transmembrane helices flatten out corresponds well with recent measurements of the effect of membrane thickness on MscL gating [79].

The Resource also modeled the effect of applied surface tension in a combined protein-membrane system. Since the protein was expected to expand, a larger membrane was required, bringing the system size to 81,044 atoms. These simulations marked the first application of non-equilibrium surface tension boundary conditions to membrane simulations. During the application of surface tension, all of the protein helices tilted to lie flatter in the plane of the membrane, while the membrane itself became thinner as it stretched. The tilt of the helices relative to the membrane normal was correlated with the decreasing membrane thickness. The transmembrane helices also tilted relative to each other in an iris-like manner, as suggested by our collaborators on the basis of structural and sequence considerations [80]. A manuscript describing the application of non-equilibrium surface tension to MscL systems is in preparation.

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

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% BRTP $: 4%

ABSTRACT: ATP synthase* is a large protein that plays a key role in the bioenergetic processes in all living cells. A transmembrane F_o unit utilizes a transmembrane electrochemical potential (proton motive force) to mechanically rotate a central stalk, causing cyclic conformational changes in the catalytic sites of a solvated F_1 unit that drive ATP synthesis. The energy conversion is nearly 100% efficient, and reversible. These remarkable properties, along with the availability of several recently obtained high resolution three-dimensional atomic structures, make ATP synthase a perfect system for exploring the energy conversion in living cells. The Resource, in collaboration with R. Fillingame, investigated the elementary chemical events (bond formation and breaking, protonation and de-protonation of key groups in F_o) and mechanical events (domain motion), involved in the energy conversion.

F_o unit. Steered molecular dynamics (SMD) simulations of the F_o unit, embedded in a lipid membrane and surrounded by water and metal ions, were performed with periodic boundary conditions. The structure included about 94,000 atoms, with 1 ns of simulation time on 256 LeMieux processors requiring 2,850 CPU-hours. Using the NAMD program [81] and different SMD protocols, we investigated how protonation and de-protonation of key residues in the rotor are coupled to a mechanical rotation of the rotor relative to the stator as well as rotation of individual transmembrane helices therein [82,83]. These simulations provided preliminary data on the energy barriers and friction coefficients for rotation. The obtained data were used to develop a novel analytical stochastic model of the F_o unit, which allowed to extend the available modeling time scale to milliseconds. In the course of the work, the Resource developed novel methods for generating lipid membranes, solvating, and ionizing proteins, which are now commonly used in several research groups.

F_1 unit. We have performed molecular dynamics simulations on a 327,000 atom system consisting of ATP synthase F_1, nucleotides, water, and ions. The simulations employed a modified form of our SMD torque application method [84] to describe the torque that the F_o subunit normally applies to F_1 in fully assembled ATP synthase. In 10.5 ns of simulation, the stalk was rotated by 250°. The torqued system displays propagation of twist along the central stalk and accompanying synthesis-like events — stalk-subunit interactions, opening and closing of the catalytic subunit, and opening of the catalytic binding site — that are consistent with the cyclic conformational transformation required for ATP synthase function.

*URL: `http://www.ks.uiuc.edu/~ilya/ATPase/index.html`

BTA UNIT: C, T

TITLE: Retinal proteins

KEYWORDS: rhodopsin, purple membrane, QM/MM, early intermediates, spectral tuning

AXIS I: 7a, 25b

AXIS II: 74h, 89

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% BRTP $: BTA 6%

ABSTRACT: Retinal proteins* function as light transducers and energy converters. In visual receptors of the eye, photo-isomerization of the retinal chromophore induces a signaling state of the protein that is biochemically amplified through interaction with the G protein transducin. The absorption spectra of the chromophore in the visual receptors are tuned by interaction with its protein environment; mutations of the green and red pigments cause the common X-linked color visual defects. In bacteriorhodopsin (bR) of archaeal bacteria, the energy of the absorbed light is used, through the isomerization of the chromophore and a well-defined series of thermal reactions, to pump protons and establish an electrochemical gradient across the cell membrane. Recently, atomic structures of bR, sensory rhodopsin II (sRII), and rhodopsin have been solved by X-ray cryatellography at high resolutions [85–89]. The availability of these structures opens the door to investigate molecular mechanisms of the signaling and energy converting processes as well as the spectral tuning.

During the funding period, the Resource has investigated different functional aspects of retinal proteins. A complete model of the purple membrane of *Halobacterium salinarum* was constructed for the first time [90]. The model consists of three monomeric bR, 28 lipid, and 2804 water molecules, altogether 24,000 atoms. It was equilibrated by constant temperature-pressure molecular dynamics (MD) simulations with hexagonal periodic boundary conditions using the program NAMD2 [16]. Conformation of the retinal chromophore in bR was examined by MD simulations, which revealed large twists around double bonds of the chromophore [91]. Early intermediates of bR's photocycle were also modeled by means of *ab initio* quantum mechanical/molecular mechanical (QM/MM) and MD simulations [92]. The resultant structures show significant conformational changes of the chromophore and hydrogen-bond network which are suggested to play a key role in the proton

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

transfer process in the later steps of the photocycle. In collaboration with E. Landau, University of Texas, the mechanism of spectral tuning in bR and sRII was investigated by the QM/MM technique [47]. The results successfully reproduced the experimental observations and explained the structural determinants of the spectral shift.

BTA UNIT: C, T

TITLE: Fluorescent Folding Probe for SH3

KEYWORDS: Protein Folding, Tryptophan, Fluorescence, Fluorescence maximum, β-sheet, WW domain, SH3

AXIS I: 2,9

AXIS II: 74h,77

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% BRTP $: BTA 2%

ABSTRACT: Fluorescence maximum, λ_{max}, can be used to characterize the state of proteins. Generally, a protein with buried tryptophans redshifts its spectra upon unfolding. λ_{max} of buried tryptophan residues occurs near 330 nm as compared to fully solvated tryptophan with λ_{max} near 350 nm [93]. Unfortunately, not all the proteins in nature have buried tryptophans. SH3 is an example where all tryptophans in the protein are exposed to the solvent. Our collaborators would like to investigate this biomolecule after their successful kinetics studies on the pin-WW domain [94]. SH3 is a small β-sheet protein with 59 residues, whereas human pin-WW domain has 34 residues. Although the sequences of both polypeptides are not similar, the structure of the WW domain can be overlapped with one region of the SH3 structure [95]. The detailed analysis of the WW domain can be compared with similar studies on SH3, elucidating the role that structure plays in protein folding. At this moment, SH3 can not be studied by our collaborators with their fluorescence detection techniques [96, 97].

Ab initio calculations have suggested that λ_{max} is sensitive to the average electric field along the long axis of Trp (E_x) [98,99]. The Resource has tested this hypothesis using full atom MD on myoglobin, monellin and 3-methylindole. The results confirm that indeed there is a trend between the computed E_x and observed λ_{max}. Using this approach, the Resource has designed surface mutations that decrease the computed

E_x for SH3. Surface mutations will not drastically change the structure of the protein, a requirement for this study.

The Resource conducted simulations of several mutants of SH3. The solvated systems contained about 10,000 atoms. MD runs were carried out using NAMD2 [81]; visualization and analysis of the simulations were made using VMD [50]. Coulombic contribution was simulated in detail by computing full electrostatics each 4 fs. Each mutant was simulated for 1 ns, given the fluorescence time scale of 10 ns. After several combinations of mutants, the Resource was able to significantly decrease E_x by mutating only one surface residue.

BTA UNIT: C

TITLE: Robustness and Optimality of Light-Harvesting in Photosystem I

KEYWORDS: bioenergetics, photosynthesis, optimality

AXIS I: 7a, 8, 9

AXIS II: 77, 84

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% BRTP $: 3%

ABSTRACT: Bioenergetic events in the respiratory chain are difficult to study directly in eukaryotic mitochondria. Therefore much of our knowledge on these electrochemical processes are obtained by studying homologous enzymes in bacteria. As part of an ongoing study of the physical processes in the photosynthetic apparatus and its respiratory chain complexes, the Resource has collaborated with P. Fromme from Arizona State University to understand the mechanism of light-harvesting in the protein-pigment complex photosystem I (PSI) of the cyanobacterium *Synechococcus elongatus*[*].

As with most biological species, photosynthetic lifeforms have evolved to function optimally near temperatures of about 300 K where thermal disorder is significant. It remains a challenge to understand how robustness and optimality of the photosynthetic apparatus is achieved. To address this challenge, a high resolution crystallographic structure [100] furnished by our collaborators was used to construct an effective Hamiltonian for the chlorophyll aggregate of PSI. In the framework of this Hamiltonian excitation transfer dynamics and spectral properties of PSI were described. The excitation lifetime and the quantum yield in the system were calculated. Study of an ensemble of effective Hamiltonians showed that at room temperature fluctuations of site energies have little effect on excitation lifetime and quantum yield, which compare favorably with experimental results. Computational experiments revealed that the efficiency of the system was robust also against the 'pruning' of individual chlorophylls. The optimality of the arrangement of chlorophylls was characterized through the quantum yield in an ensemble of randomly oriented chlorophylls. The quantum yield was seen to change only within a narrow interval in such an ensemble. However, within that narrow interval the original arrangement of chlorophylls in PSI was found to realize nearly optimal efficiency.

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

BTA UNIT: C

TITLE: The Photosynthetic Unit of *Rhodospirillum rubrum*

KEYWORDS: Light-Harvesting Complex I, Reaction Center, Homology Modeling

AXIS I: 7a, 8, 9

AXIS II: 77, 89

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% BRTP $: 2%

ABSTRACT: The Photosynthetic Unit (PSU) of *R. rubrum* consists of a ring-like light-harvesting complex I (LH1) that surrounds the reaction center (RC) [101–103]. The LH1 ring collects light energy and funnels it towards the reaction center, where charge separation occurs. Inside the reaction center light energy is converted into chemical energy driving a cycling photosynthesis process for the generation of ATP * [104]. Unlike other purple bacteria, *R. rubrum* consists only of the core photosynthetic apparatus (LH1 and RC), but has no additional peripheral light-harvesting complexes (LH2) [101]. In fact, *R. rubrum* contains the simplest photosynthetic apparatus of all purple bacteria and the *R. rubrum* PSU forms circular-shaped complexes in the photosynthetic membrane observed by cryoelectron microscopy [101–103]. This PSU is therefore ideal as a model system for studying electron transfer properties in a natural environment containing all structurally known membrane protein components for a single organism.

The Resource constructed a structural model of the RC-LH1 complex embedded in a POPC bilayer; the solvated system contained 243,874 atoms. Both the *R. rubrum* LH1 and RC complex were constructed using homology modeling. The templates were obtained from the *Rhodobacter (Rb.) sphaeroides* LH1 model [105] and the high-resolution RC structure of *Rb. sphaeroides* [106]. The *R. rubrum* LH1

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

model is in agreement with the 8.5 Å map obtained by cryoelectron microscopy and superimposes perfectly upon it. A further structural comparison of the models with each other as well as with the available LH2 structures [107, 108] yielded strikingly similar folding motifs and a conserved binding pocket for bacteriochlorophyll a (BChla). The identity between the *R. rubrum* and *Rb. sphaeroides* RC sequence was as high as 70.2% for the L-subunit and 65.8% for the M-subunit. Also the protein environment around the photosynthetic pigments is structurally conserved in the three available RC structures from *Rb. sphaeroides* [106], *Blc. viridis* [109] and *T. tepidum* [110]. The positioning of the RC inside LH1 was performed by employing two key criteria. The first criteria was the alignment of the C_{16} symmetry axis of the LH1 complex with the pseudo C_2 symmetry axis of the RC and the second was the arrangement of RC pigments towards LH1 BChla's ensuring optimal energy transfer rates in the model. The positioning has been carried out using the program VMD [50].

Although the photosynthetic apparatus of cyanobacteria has evolved to a greater complexity in comparison to purple bacteria, the overall architecture of PSU's is strikingly similar in both domains of life [111,112]. A comparison of the RC model of *R. rubrum* and the recently solved 2.5 Å photosystem I structure from *Synechococcus elongatus* [100] show a close similarity in the orientation of pigments in the RC region of both organisms. A structural relationship between bacterial RCs and plant RCs has been already suggested by Blankenship et al. [111] and is now confirmed by the structures from photosystem I and II [100, 113]. The membrane embedded RC-LH1 complex of *R. rubrum*, which is small compared to Photosystem I of *S. elongatus* will be subjected to MD simulations carried out using NAMD2 [16].

BTA UNIT: C

TITLE: Helix association in lipid environments

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

AXIS I: 2,7a

AXIS II: 74f,h;77;89

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% BRTP $: 2.5%

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 [114–116]. Transmembrane helices embedded in micelles provide a small system in which their interaction may be studied.

We are 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-helix contacts in micellar environments. Because micelles differ in curvature and composition from natural membrane bilayers, it is also important to compare the results of helix-helix association in a micellar environment to that in a lipid bilayer.

Initial simulations of the human wild-type glycophorin A (GpA) transmembrane domain and the G83A mutant in a sodium dodecyl sulfate (SDS) micelle have been

carried out. The fully solvated systems ($\sim 30,000$ atoms) have been subject to free molecular dynamics simulations lasting 5ns. While the wild-type GpA and micelle are stable over the course of the simulation, the G83A mutant is unstable: the helices move apart and rotate with respect to one another. These findings correspond to experimental studies which demonstrate that the G83A mutation disrupts dimerization.

BTA UNIT: C

TITLE: Gold binding protein

KEYWORDS: biomineralization, gold, molecular dynamics

AXIS I: 2

AXIS II: 74h

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% BRTP $: 2%

ABSTRACT: The biological control of inorganic crystal morphology is necessary for the formation of biological hard tissue and is of use in the creation of novel materials. Sarikaya et al. have developed a genetic system to isolate proteins which control gold crystalization. It was shown [117] that in the presence of gold binding protein (GBP)*, gold formed large, flat hexagonal crystals displaying the {111} surface. No such crystals were seen to form in the presence of control proteins which do not bind to gold.

It is hypothesized that GBP binds preferentially to the {111} Au surface, and that the covering of the {111} face by the bound GBP plays a role in the mechanism by which GBP alters crystal morphology. Because the GBP sequence does not contain cysteine (known to form a covalent linkage with gold), the mechanism by which GBP adheres to gold is not readily apparent. It is also unclear why the {111} surface would be prefered to (e.g.) the more sparsely populated {112} face. Molecular dynamics simulations have been employed to elucidate the interaction.

We have predicted structures for the three GBP sequences available. Of the three proteins, two are found to have repeating motifs which may be conducive to binding to a periodic surface. Molecular dynamics simulations lasting four nanoseconds

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

of fully solvated GBP on both the {111} and {112} crystal surfaces ($\sim$ 30000 atoms) have been carried out using NAMD [118]. The dynamics show that the close contacts to gold originate from the polar sidechains. Additionally, water is found to diffuse in the surface corrugations of the {112} surface, hindering the interaction [119].

BTA UNIT: T

TITLE: Quantum Biology

KEYWORDS: Photobiology, Semiempirical Methods, QM/MM

AXIS I: 7a,25b

AXIS II: 74h,77

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% BRTP $: 4.5%

ABSTRACT: Quantum mechanical effects can be important in biological processes, especially those involving either proton transfer or electronic excitation. The Resource has developed several highly promising new methods for quantum biology over the last funding period. The multiple spawning method for photobiology has been developed [120, 121] and applied to investigate the short time dynamics of photoisomerization in retinal protonated Schiff base [122] (RPSB) and bacteriorhodopsin [123]. The *ab initio* multiple spawning method which couples quantum chemistry directly to multiple spawning dynamics has been developed and applied [124–129] to several paradigmatic cis-trans photoisomerization chromophores which serve as models for the photoisomerization process that triggers visual response. The Resource has also extended multiple spawning dynamics to treat tunneling effects [130] such as can be important in proton transfer, and developed a first-principles variant of this method which directly computes electronic structure as needed [131].

The Resource has used sophisticated quantum chemistry methods to elucidate the ground and excited state potential energy surfaces of the retinal protonated Schiff base which forms the primary chromophore in many photoactive proteins [132,133]. Retinal protonated Schiff base has five double bonds capable of undergoing isomerization. Upon absorption of light, the chromophore isomerizes and the character of the photoproducts (e.g. 13-cis and 11-cis) depends on the environment, protein vs. solution. Our *ab initio* calculations show that in the absence of any specific interactions with the environment (e.g. discrete ordered charges in a protein) energetic considerations cannot explain the observed bond selectivity. We instead attribute the origin of the bond selectivity to the shape (topography) of the potential energy surfaces in the vicinity of points of true degeneracy (conical intersections) between the ground and first excited electronic states. This was the first reported molecular example where a competition between two distinct but nearly isoenergetic photochemical reaction pathways is resolved by a topographical difference between two conical intersections, and may be an important factor in understanding protein-induced selectivity in photoisomerization.

The Resource has also pursued the development of new methods for describing molecular potential energy surfaces in order to ultimately apply the first principles simulation techniques directly to dynamics in photoactive proteins. We developed a new approach to describe Pauli repulsion between parts of a molecule treated quantum mechanically and with force fields [134]. We have developed furthermore a new approach to force fields incorporating polarization and/or charge transfer [135]. We recently implemented a minimal energy conical intersection (MECI) optimization algorithm within the context of semiempirical methods [136]. Computationally, this semiempirical conical intersection optimization method is much less demanding than *ab initio* techniques. We applied the method to several molecules and compared

the geometries and energies of the resulting MECIs with *ab initio* methods. The locations of the semiempirical MECIs agreed very well with the *ab initio* predictions, but the energetics generally did not. This suggests that the semiempirical conical intersection optimization method may be useful in finding initial guess geometries for *ab initio* MECI searches and/or in identifying families of MECIs which may be relevant in photochemical dynamics. The good agreement of MECIs locations further suggests that in many cases, reparameterization of semiempirical methods to reproduce both energetics and locations of MECIs may be successful. Indeed, we have already carried this out for the RPSB molecule and the chromophore of Green Fluorescent Protein (GFP). We have also completed a QM/MM implementation interfaced to the reparameterized semiempirical method and begun simulations of the photodynamics of the GFP chromophore in water.

BTA UNIT: C, D

TITLE: Computational Facility

KEYWORDS: parallel computing, visualization, network

AXIS I: 11

AXIS II: 42,89

INVEST1: Tim Skirvin

DEGREE1: B.S.

DEPT1: Theoretical Biophysics

NONHOST1:

% BRTP $: 9%

ABSTRACT: The last five years have seen the Resource vastly improve its computational facility* in four major categories: the acquisition of graphical workstations for every desktop, a large increase in computational power with a shift towards cluster computing, a standardization and stabilization of our back-end servers, and a move to disseminate information using web-backed databases. These changes have allowed us to simulate and analyze ever-larger molecular systems, and to better maintain our local resources. The group currently has 43 local users, and 103 overall.

The largest change in the last five years has been the proliferation of 3D-capable graphics workstations to all researcher desktops. We currently have a total of 53 3D-capable workstations, up from just 8 five years ago; 43 are on researcher desktops, and the remaining 10 are available for public use. This was made possible both by the drop in the cost of computers in the last five years, and the effective recycling of machines previously used for our computation clusters. At this time, every Resource researcher has a 3D-capable workstation on his or her desk.

The last five years have also seen a vast increase in the amount of local computational power. Through the use of inexpensive yet powerful Linux clusters, we now have nearly 10 times as many computers locally available, offering us 16 times the computer time of five years ago. These clusters are extremely well-utilized thanks to the use of the Scyld Linux cluster management system.

Our servers have become extremely stable and standardized over the last five years. Through the use of five redundant Sun Enterprise 250 servers, we have been able to dramatically increase stability and security for all Resource data. These servers

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

currently share 2.75TB of data to more than 100 clients across gigabit and 100 megabit ethernet networks. This data is backed up nightly using four DLT tape changers and an in-house software package. Additional services, such as mail and web, are managed using Sun Ultra 5 and Netra X1 systems.

In the past five years supercomputer time allocations awarded to the Resource have increased by a factor of 50.

Resource Summary (2001–2002)

	TECH RES & DEVEL (T)	COLLAB RES & SERVICE (C)	DISSEM & TRAINING (D)	TOTALS
NUMBER OF PUBLICATIONS	12	14	6	32
NUMBER OF SUBPROJECTS	6	12	5	23*
NUMBER OF INVESTIGATORS	32	19	16	67*
PERCENT OF BRTP FUNDS ALLOCATED	45.25%	26.25%	28.5%	100%†
SERVICE FEES COLLECTED	0	0	0	0
OTHER FUNDS ($)	$50,000	$200,000	$25,000	$275,000

*Investigators and subprojects classified in more than one BRTP unit are counted twice.

† Percentages may include membership in multiple categories.

Geographical Data (2001–2002)

State or Country	Number of Investigators
IL	35
WA	1
CA	1
MO	1
MN	1
WI	1
TX	2
Germany	2
Israel	1
Japan	1
Italy	1
UK	1
Denmark	1

BRTP Unit T (2001–2002)

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Aksimentiev, Aleksei	University of Illinois (Schulten, Klaus)	FED	NIH
Bach, Michael	University of Illinois (Schulten, Klaus)	FED	NIH
Balabin, Ilya	University of Illinois (Schulten, Klaus)	FED	NIH NSF
Ben-Nun, Michal	University of Illinois (Martinez, Todd)	FED	NIH
Brandon, David	University of Illinois (Budescu, Gila)	FED	NIH
Brunner, Robert	University of Illinois (Kale, Laxmikant)	FED	NIH
DeSouza, Jayant	University of Illinois (Kale, Laxmikant)	FED	NIH
Dittrich, Markus	University of Illinois (Schulten, Klaus)	OTH	
Fillingame, Robert	University of Wisconsin, Madison (Fillingame, Robert)	OTH	
Grayson, Paul	University of Illinois (Schulten, Klaus)	FED	NIH
Gruebele, Martin	University of Illinois	FED	NIH
Gullingsrud, Justin	University of Illinois (Schulten, Klaus)	FED	NIH
Hardy, David	University of Illinois (Skeel, Robert)	OTH	
Hayashi, Shigehiko	University of Illinois (Schulten, Klaus)	OTH	
Isralewitz, Barry	University of Illinois (Schulten, Klaus)	FED	NIH

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Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Kandori, Hideko	Kyoto University, Japan (Kandori, Hideko)	OTH	
Kumar, Sameer	University of Illinois (Kale, Laxmikant)	FED	NIH
Larios, Edgar	University of Illinois (Schulten, Klaus)	OTH	
Morales, Jorge	University of Illinois (Martinez, Todd)	OTH	
Olivucci, Massimo	Univeersity of Sienna, Siena, Italy (Olivucci, Massimo)	OTH	
Olsen, Seth	University of Illinois (Martinez, Todd)	OTH	
Phillips, James	University of Illinois (Schulten, Klaus)	FED	NIH
Ritz, Thorsten	Virginia Polytech Institute	OTH	
Sheves, Mordechai	Weizmann Institute, Rehovot, Israel (Sheves, Mordechai)	OTH	
Stone, John	University of Illinois (Schulten, Klaus)	FED	NIH
Suhai, Sandor	German Cancer Res. Inst., Heidelberg (Suhai, Sandor)	OTH	
Tajkhorshid, Emadeddin	University of Illinois (Schulten, Klaus)	FED OTH	NIH
Toniolo, Allesandro	University of Illinois (Todd Martinez)	OTH	
Unger, Joshua	University of Illinois (Kale, Laxmikant)	FED	NIH
Vandivort, Kirby	University of Illinois (Schulten, Klaus)	FED	NIH
Wang, Hui	University of Illinois (Schulten, Klaus)	FED	NIH
Zheng, Gengbin	University of Illinois (Kale, Laxmikant)	FED	NIH

BRTP Unit C (2001–2002)

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Aksimentiev, Aleksei	University of Illinois (Schulten, Klaus)	FED	NIH
Autenrieth, Felix	University of Illinois (Schulten, Klaus)	OTH	
Bach, Michael	University of Illinois (Schulten, Klaus)	FED	NIH
Balabin, Ilya	University of Illinois (Schulten, Klaus)	FED	NIH NSF
Brandon, David	University of Illinois (Budescu, Gila)	FED	NIH
Braun, Rosemary	University of Illinois (Schulten, Klaus)	OTH	
Brunner, Robert	University of Illinois (Kale, Laxmikant)	FED	NIH
DeSouza, Jayant	University of Illinois (Kale, Laxmikant)	FED	NIH
Dittrich, Markus	University of Illinois (Schulten, Klaus)	OTH	
Fernandez, Julio	Mayo Clinic (Fernandez, Julio)	FED	NIH
Fillingame, Robert	University of Wisconsin, Madison (Fillingame, Robert)	OTH	
Fromme, Petra	Arizona State University	OTH	
Gao, Mu	University of Illinois (Schulten, Klaus)	OTH	
Grayson, Paul	University of Illinois (Schulten, Klaus)	FED	NIH
Gruebele, Martin	University of Illinois	FED	NIH

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Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Gullingsrud, Justin	University of Illinois (Schulten, Klaus)	FED	NIH
Hayashi, Shigehiko	University of Illinois (Schulten, Klaus)	OTH	
Isralewitz, Barry	University of Illinois (Schulten, Klaus)	FED	NIH
Izaguirre, Jesus	University of Notre Dame	OTH	
Jensen, Morten	Technical University of Denmark (Schulten, Klaus)	OTH	
Kandori, Hideko	Kyoto University, Japan (Kandori, Hideko)	OTH	
Kumar, Sameer	University of Illinois (Kale, Laxmikant)	FED	NIH
Landau, Ehud M.	University of Texas Medical Branch (Landau, Ehud M.)	OTH	
Larios, Edgar	University of Illinois (Schulten, Klaus)	OTH	
Lu, Deyu	University of Illinois (Schulten, Klaus)	FED	NIH
Lu, Hui	Danforth Plant Science Center (Skolnick, Jeff)	OTH	
Olivucci, Massimo	Univeersity of Sienna, Siena, Italy (Olivucci, Massimo)	OTH	
Park, Sanghyun	University of Illinois (Schulten, Klaus)	FED	NIH
Saam, Jan	Humboldt University, Berlin, Germany (Schulten, Klaus)	OTH	
Sener, Melih	University of Illinois (Schulten, Klaus)	FED	NIH
Sheves, Mordechai	Weizmann Institute, Rehovot, Israel (Sheves, Mordechai)	OTH	
Skirvin, Tim	University of Illinois (Schulten, Klaus)	FED	NIH
Stroud, Robert	University of California, San Francisco	OTH	

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Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
	(Stroud, Robert)		
Suhai, Sandor	German Cancer Res. Inst., Heidelberg (Suhai, Sandor)	OTH	
Tajkhorshid, Emadeddin	University of Illinois (Schulten, Klaus)	FED OTH	NIH
Tietz, Carston	University of Stuttgart	OTH	
Vandivort, Kirby	University of Illinois (Schulten, Klaus)	FED	NIH
Vogel, Viola	University of Washington	FED	NIH
Wang, Hui	University of Illinois (Schulten, Klaus)	FED	NIH
Zhu, Fangqiang	University of Illinois (Schulten, Klaus)	OTH	

BRTP Unit D (2001–2002)

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Bach, Michael	University of Illinois (Schulten, Klaus)	FED	NIH
Brandon, David	University of Illinois (Budescu, Gila)	FED	NIH
Brunner, Robert	University of Illinois (Kale, Laxmikant)	FED	NIH
DeSouza, Jayant	University of Illinois (Kale, Laxmikant)	FED	NIH
Grayson, Paul	University of Illinois (Schulten, Klaus)	FED	NIH
Gullingsrud, Justin	University of Illinois (Schulten, Klaus)	FED	NIH
Hardy, David	University of Illinois (Skeel, Robert)	OTH	
Kumar, Sameer	University of Illinois (Kale, Laxmikant)	FED	NIH
Isralewitz, Barry	University of Illinois (Schulten, Klaus)	FED	NIH
Phillips, James	University of Illinois (Schulten, Klaus)	FED	NIH
Skirvin, Tim	University of Illinois (Schulten, Klaus)	FED	NIH
Stone, John	University of Illinois (Schulten, Klaus)	FED	NIH
Unger, Joshua	University of Illinois (Kale, Laxmikant)	FED	NIH
Vandivort, Kirby	University of Illinois (Schulten, Klaus)	FED	NIH
Wang, Hui	University of Illinois (Schulten, Klaus)	FED	NIH
Zheng, Gengbin	University of Illinois (Kale, Laxmikant)	FED	NIH

Advisory Committee

The Resource Advisory Board met on May 2, 2001, and produced the following report (also included in last year report). Following a visit in March 2002 to assess the Resource renewal request, our site visit panel produced a Summary Statement, which is included at the end of this report.

The members of the Advisory Board are:

- Jeff Skolnick, Danforth Plant Science Center, Chair
- Angel Garcia, LANL
- Angela Gronenborn, NIH
- Benoit Roux, Cornell Medical School
- Marc Snir, IBM (now at UIUC)

The advisory committee of the University of Illinois' NIH Resource for Macromolecular Modeling and Bioinformatics under the direction of the PI, Klaus Schulten held its annual meeting on May 2, 2001 with all committee members, Drs. Angel Garcia, Angela Gronenborn, Benoit Roux, Marc Snir and Jeff Skolnick, chairperson, attending. The committee was uniformly enthusiastic about the quality of research done at this resource and recognized the unique and important approach of this resource to perform state of the art defining molecular dynamics simulations on very large systems. This research resource has a very strong list of both national and international collaborators. Furthermore, it has a vigorous training service, training and dissemination effort. Thus, all aspects required of a research resource were strongly addressed.

The presentation by John Stone about VMD was favorably received. There have been almost 10,000 downloads of this program since April 2000. VMD has been successfully ported to all major computer platforms. The use of python scripting was favorably reviewed. Furthermore, Barry Isralewitz gave an overview of proposed powerful extensions of VMD to include sequence processing tools, fragment identification and the proposed incorporation of structure alignment and other web based sequence tools which was very favorably received. This effort was viewed very positively and is strongly encouraged.

The BioCoRE project develops a portal that will facilitate resource sharing and collaboration among geographically distributed teams of biomedical researchers. This includes support for remote job submission and monitoring, shared visualization, sharing of simulation data, etc.

The BioCoRE project already has much functionality that can clearly benefit researchers – especially the support for simultaneous visualization, remote job submission, and distributed file system. It can already provide a reasonably complete environment for collaborative work in molecular simulations. However, the system is new and there is still little evidence of its usefulness to end users. It is important to work closely with a user community so as to validate and refine the design. The planned collaboration with the NSF Grid community will enable BioCoRE to focus on the specific requirements of the biomedical community, while using a generic grid infrastructure for core services.

The program NAMD is an object-oriented molecular dynamics parallel code designed for high-performance simulations of large biomolecular systems. It is distributed free of charge and includes source code. It has two main advantages: the very high scalability in parallelization (hundreds of CPUs), and the modularity of the source code (written in C++). The first advantage is important because the availability of large number of relatively inexpensive computers is expected to increase. The second advantage is also very important since it allows potential users and collaborators to implement new computational methodologies in the code without disrupting the structure of the program. Despite the impressive performance of NAMD, it appears to be very difficult to spread its usage throughout the scientific community (which remains dominated by AMBER, CHARMM, and GROMOS). It might be a good idea to organize additional practical workshops to decrease the barriers for using a new program.

Turning to steered molecular dynamics, several projects are under investigation; all are of outstanding scientific interest and executed at the highest level of competence.

- Unfolding of Titin; Excellent integration of experimental results(mechanical unfolding by FM) and simulation. Good example of cross-fertilization between experimentalists and modelers.
- Mechanosensitive channels; surface tension is applied in the simulation and results in tilting of the helices with concomitant expansion of the protein structure. An expansion of the channel has been suggested from experimental results.
- ATP synthase; this is an excellent example of a molecular machine. The simulation in this case is a steered MD simulation using torque. Observations from the simulation results can help explain the mechanism of the machine.

A natural extension of the steered MD simulation involves the use of a haptic interface in interactive MD. Real time force feedback allows the user to experience a sensation of the mechanical properties of the system.

The BioCoRE project develops a portal that will facilitate resource sharing and collaboration among geographically distributed teams of biomedical researchers. This includes

support for remote job submission and monitoring, shared visualization, sharing of simulation data, etc. The BioCoRE project already has much functionality that can clearly benefit researchers— especially the support for simultaneous visualization, remote job submission, and distributed file system. It can already provide a reasonably complete environment for collaborative work in molecular simulations. However, the system is new it will be important to work closely with a user community so as to validate and refine the design. The planned collaboration with the NSF Grid community will enable BioCoRE to focus on the specific requirements of the biomedical community, while using generic grid infrastructure for core services.

An impressive number of outstanding research collaborations, both within the institution as well as with researchers throughout the US and world is carried out by the Resource. For example, the project on protein-DNA aggregates combines coarse grained models with all atom models. This is an excellent way to get at large protein-nucleic acid assemblies. In particular the nucleosome, all enzymes that intimately work on DNA topology like recombinases and topoisomerases are ideal candidates for this approach.

The dissemination of software is one strong component of service of this research resource. There are 7 programs, NAMD, VMD, BioCoRE, JMV, MDTools, MDSalon and BiosoftDB available for downloading. The service component is highly rated by the users, with 92% reporting that VMD meets their needs, for example.

As part of their service efforts, they had 22 seminars, provided extensive user support, had 9 visitor and 45 external users occupying 10% of the local disk space. This is an extensive service effort.

With respect to dissemination, this resource has expended considerable effort to update their web site. They published 32 papers, gave 55 talks and 15 posters, prepared brochures, and videos, have appeared in trade magazines, printed media and have issued press releases. This is a vigorous effort.

Overall this is an outstanding resource that is developing, applying and disseminating state of the art approaches for computational biology.

Organization

In the past five years the Resource has made web technologies its key management tool. In the process we have redesigned the Resource web site and adopted a more contemporary look, while at the same time adding functionality, keeping the simplicity, and enriching content and substance.

We are continuing to transfer 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; we are yet to transfer additional services to the web, from user account creation and management and a more sophisticated web-based management system, to tracking of talks and seminars.

We value, and adopted very early on, the extensive use of the web for management and information sharing, as well as other technologies such as databases. Just like our approach toward cluster computing, we always seek to take advantage of any proven and creative cost-effective solutions that we think would improve administration and daily operation and yet, would cost less and be simple to integrate. The Resource's web site represents our way of seeing and doing things both within and beyond the Resource's formal boundaries.

Organizational Structure

The Resource's organizational structure is determined by its mission and nature of activities. It is shown in Fig. 7.

K. Schulten is the Principal Investigator and Program Director of the Resource. R. Skeel, L. Kalé and T. Martínez as well as G. Budescu are Co-Principal Investigators. The Resource is located at the Beckman Institute for Advanced Science and Technology and K. Schulten, the Resource Director, administratively reports to the Institute Director. The Institute Director reports to the University of Illinois Vice Chancellor for Research. The Advisory Committee monitors Resource activity and provides highly relevant information and experienced guidance on the scientific scope and directions of the Resource.

The Resource researchers come from a spectrum of disciplines, each of which contributes significantly to the intricate fabric of the Resource goals and activities. The graduate assistants are affiliated with departments such as Physics, Computer Science, Biophysics, Chemistry, and Electrical and Computer Engineering.

All Resource members are involved in the daily operation of the facility. Members attend weekly group and subgroup meetings, are responsible for specific maintenance tasks at the Resource, participate and present talks in group seminars, and keep continuously

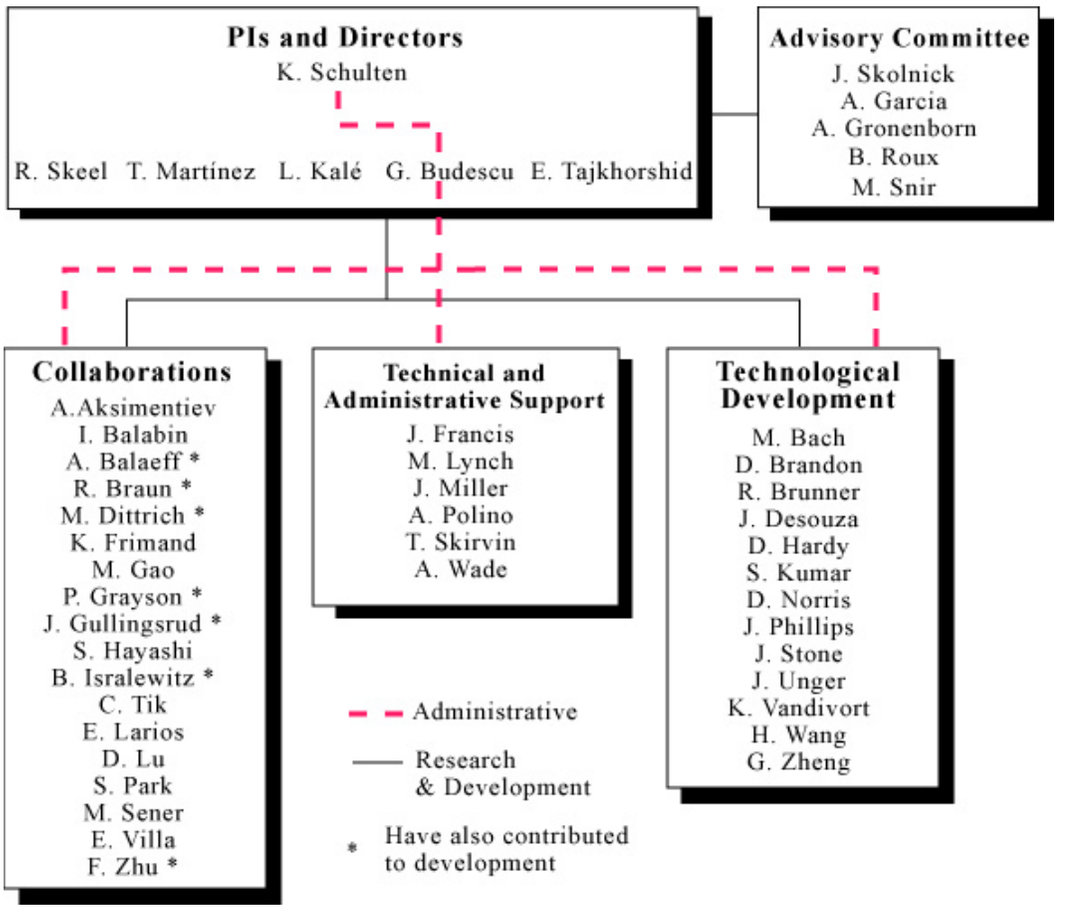

Figure 7: Resource organizational structure

informed 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 in consultation with the researchers. 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 progress and adherence to the criteria outlined above. Computer time is allocated to the projects as needed.

The Resource's administration has kept abreast of technological changes. All paperwork, communication, routine working plans, and special activities are kept in electronic form and are accessible online. The ongoing development of the Resource web site and careful attention to details of design and contents have made the Resource's internal site an effective and novel administrative instrument. The site contains all relevant information for new and old Resource members in a well-structured form and is a prime example of unobtrusive management.

The web-based Resource manual serves as an introductory guide for new members and as a reference source for old members. The continually evolving manual 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. The list is designed to streamline and systematize the Resource operation. The manual offers tips and information on the Resource's internal processes, and on Beckman and UIUC facilities and procedures.

How to Acknowledge Resource Support

Resource's users and beneficiaries are required to acknowledge Resource support in several ways*, depending on the resources used:

1. When using the Resource's compute power and/or expertise, and/or Resource software for their research/training/other, users are expected to include the following statement in their resulting work:

   "This work was supported by the Theoretical Biophysics group, an NIH Resource for Macromolecular Modeling and Bioinformatics, at the Beckman Institute, University of Illinois at Urbana-Champaign."

   If the work is made available online users and beneficiaries are expected to make a link to the Resource web site (`http://www.ks.uiuc.edu/`)

2. When using images produced by the Resource, users and beneficiaries are required to include in their publication the following statement:

   "This image was made by the Theoretical Biophysics group, an NIH Resource for Macromolecular Modeling and Bioinformatics, at the Beckman Institute, University of Illinois at Urbana-Champaign."

   If the image was published in a Resource publication, you are required to get a permission from the Resource, from the publisher and to reference the relevant paper.

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

If their publication is made available online users are expected to make the following links to our web site:

- required link to the original image on our site
- if the image was published in a Resource publication, required link to the relevant paper
- optional link to `http://www.ks.uiuc.edu/`

3. When using images produced with Resource software (VMD, NAMD, other), users and beneficiaries are required to include in their publication the following statement:

   "This image was made with VMD/NAMD/other software support by the Theoretical Biophysics group, an NIH Resource for Macromolecular Modeling and Bioinformatics, at the Beckman Institute, University of Illinois at Urbana-Champaign."

   If the image was published in a Resource publication, you are required to get a permission from the Resource, from the publisher and to reference the relevant paper.

   If their publication is made available online users are expected to make the following links to our web site:

   - required link to the original image on our site
   - required link to VMD/NAMD/other relevant Resource software pages
   - if the image was published in a Resource publication, required link to the relevant paper
   - optional link to `http://www.ks.uiuc.edu/`

Service, Training and Dissemination

Our Research and Development core activities are translated into operational terms that fall into two general operational areas: development work to create research tools and methods, and collaborations that use the tools to facilitate research. Both of these activity areas have vast potential and practical implications for the Resource and the biomedical community at large. Through service, training and dissemination we transfer the outcomes and deliver the technologies to the community and to specific target groups such as scientists at other universities and research institutions, government and industrial organizations, as well as the general public.

Our service, training, and dissemination can be thought of as boundary spanning mechanisms through which we merge with our environment in a formal way. The Resource is an elastic entity that can expand/shrink in rapid response to internal and external changes.

The fusion of powerful environmental forces critical and beneficial to our survival have redefined our direction and decision making in recent years and are the backdrop for the way we do and will do things in the coming years. They are:

- the huge genomic data revolution and the increasing pace of structure discovery
- the explosive hardware development (much more computing power for much lower cost)
- the web technology

These forces and 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 unprecedented— 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 along with that, the service, training and dissemination opportunities, and the complexity of our relationship with our environment have widened tremendously. We initiated the Resource's use of the web for research and development purposes as well as for administration and management as early as 1994; over the past funding cycle we have completed the move of all possible Resource-related information to the web, either onto our web site for public consumption or to our internal site for local use.

In the past five years we have made web technologies our key service, training and dissemination tools. In the process we have redesigned the Resource web site and adopted

a more contemporary look, while at the same time adding functionality, keeping the simplicity, and enriching content and substance.

Organization boundaries, once well defined and rigid, have become blurry and flexible, thereby impacting our strategic thinking and daily operation. Immense opportunities for better administration, service, training and dissemination have opened and with them new secondary issues of intellectual property, copyright matters, licensing etc. are addressed and handled.

Two new features on our web site are particularly indicative of our efforts and underlying approach to the planning, coordination and implemention of service, training and dissemination:

1. A monthly research highlight anchors our front page in a clear biomedical context. The Previous Highlights section offers the visitor recently published examples of Resource work and some sense of overview. This section has also a very practical function— it allows a rapid response when the Resource is asked to provide highlights to various agencies and centers on and off campus.

2. The new face of our web-based publication section relies on our publication database, which stores data on our entire publication process, from the first submission through proof revision and reprint distribution. The database allows the Resource to document every publication-related action, share full information with other co-authors, and, once papers are in press, make them available in abstract and full PDF format from our web site, with full attention to copyright laws that govern distribution. A search function, facilitated by the database back end, is another friendly feature turning our publication section into an easily accessible library. As with the rest of the site, here too we have sought functionality, form and content with special emphasis on simplicity. The process allows for all new submissions to end up on the web as soon as they are accepted for publication. This helps us with the actual publication process, making it much easier for others to get access to our published work, and consequently has greatly widened the distribution and impact of our work.

Through the successful use of the web for service, training and dissemination we reach the widest possible audience. Access to our extensive web resources allows users to hear of us, read about us and learn to use the variety of tools, expertise and knowledge produced at the Resource.

While in the past our focus was mostly on web-based dissemination and services, in the future we intend to substantially expand and develop our web-based training opportunities. The growing functionality and popularity of BioCoRE and of high bandwidth communication networks make this goal timely, effective and relevant.

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 for its effective support of collaborations, as evidenced by the completed and undergoing collaborative projects outlined earlier.

Computational Resources In the past five years the Resource's computational facility has benefited members, their collaborators, and others with research projects related to Resource expertise and areas of study.

More than 100 researchers use the Resource's computational facilities. The Resource has increased its local computational power by a factor of 16 since 1997. In that same period, the Resource increased its use of external supercomputer time allocations by a factor of 50. The Resource's local visualization capacity has grown by 6.6 times of what it was in 1997, and local disk storage capacity has increased to 21 times the 1997 capacity.

We share our local resources with other groups whenever possible and appropriate—currently our systems have 60 external users, with approximately 15% of our disk space used by these users. Our knowledge of visualization equipment, large-memory computers, and computational clusters has been of specific use to the world at large; several sites have requested and received advice regarding the acquisition and set-up of such equipment and gone on to purchase similar systems and solutions for their local utilization. These include the UIUC Beckman Institute, the UIUC School of Chemical Sciences, Prof. Bruinsima at UCLA, Prof. Walker at Cambridge, Prof. Fernandez at Mayo Clinic, Prof. Skolnick at The Danforth Plant Science Center (St. Louis), The German Cancer Research Center (Heidelberg), and others.

Resource Collaborations Through collaborations between members and experimentalists, the Resource provides services to groups and individuals who lack the computational resources and skills themselves. More details on the content and scope of the Resource collaborative projects are provided earlier in this final report. We would like to stress here that the efforts invested by the Resource to support experimental work are mutually beneficial to the Resource and to the non-Resource scientists. Our mission is greatly enhanced through partnerships with scientists who are involved in experimental studies with direct and immediate relevance to the health of the nation. The collaborations anchor the Resource efforts in a highly relevant context and ensure that our researchers are always aware of the vital need to apply their knowledge to real-world challenges.

Resource Software The Resource is engaged in intensive technology transfer and distributes 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 single simple yet sophisticated distribution mechanism we use for the Resource lead programs.

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 user may then install the software at their leisure. All registration information and download data are stored in a local database, and can be easily mined for 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. Statistics on NAMD, VMD and BioCoRE, our flagship programs, will be presented later in this section. Here we would like to give a picture of our overall software offerings, which have dramatically increased towards the end of this funding cycle, starting with our smaller packages.

JMV[*] is a molecular viewer written in Java and Java3D. JMV is designed to be an easy-to-use, platform neutral, molecular visualization tool, which can be used standalone, as an applet in a web page, or integrated in a larger program.

MDTools[†] is a collection of programs, scripts, and utilities we provide for researchers to make various modeling and simulation tasks easier, and furnishing basic code and utilities which can be built up into larger tool sets.

[*] `http://www.ks.uiuc.edu/Development/jmv/`

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

MDSalon[‡] is an interactive forum where molecular dynamics practitioners and developers of all experience levels, to exchange ideas. Users are urged to read any of the discussion forums and to post their questions, comments, ideas.

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 already contains 328 programs which are of interest to researchers in the fields of structural biology, quantum chemistry, and bioinformatics. As of the end of September 2001, it had over 8,509 unique visits.

Use of VMD, NAMD, and BioCoRE The Resource web site is a leading information and education center in molecular biomedicine and a widely recognized distribution resource for biomedical software.

Since we began full record keeping in January 2000, the number of VMD registrants across the most recent versions has reached 18,583 with 3,989 repeat users (repeat users are represented once in the total number of registrations). 3,127 VMD users are NIH funded. NAMD has registered 3691 users (716 repeats) with 552 of them NIH funded, and BioCoRE has attracted 432 users, working on 95 projects, 42 of which are NIH funded. The past 2.5 years (1/7/2000–5/6/2002) have shown more than 45,000 VMD downloads and more than 10,000 downloads for NAMD.

The software release schedule of the Resource's lead programs boasts great productivity and lively activity with 4 and 2 major releases for NAMD and VMD respectively since 10/2001. Following its initial release, BioCoRE updates have been released weekly.

NAMD was included in the newly released Scyld Beowulf CD[¶], bringing it to a much larger and heterogeneous population of users. We are considering the possibility of including VMD in a similar release of OpenOSX[‖] and other similar vendors in the US and overseas.

We are discussing with industry (Vertex Pharmaceuticals, 3-Dimensional Pharmaceuticals, Inc., BASF, others) collaborative projects and special licenses for our software.

The improved appeal and usability of the Resource web site has led to consistently growing numbers of unique visits, with each quarter in the past year posting a significant increase of visitors. (A visitor is defined as an individual machine accessing a web page on our

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

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

[¶] `http://www.scyld.com/`

[‖] `http://www.openosx.com/`

site; note that this is a much more conservative and accurate method of measuring web traffic than web hits) Between Fall 2000 and Spring 2002 the average number of visitors to our site was 22,500/month. The total number of unique visitors to the Resource web site in the past year is 269,964.

The visitor distribution (by major section) in the past year reflects best the popularity of te Resource site:

	Visitors to site		Total Visitors
VMD	8,250 / month	(8,224)	98,688
NAMD	3,250 / month	(3,229)	38,748
BioCoRE	800 / month	(821)	9,852
Other Research	5,000 / month	(4,973)	59,676
Papers	1,800 / month	(1,821)	21,852
galleries	1,200 / month	(1,221)	14,652
seminars	300 / month	(329)	3,948
total	22,500 / month	(22,497)	269,964

NAMD, VMD and BioCoRE Accomplishments

NAMD Recent NAMD accomplishments include:

- NAMD incorporates new simulation capabilities. Input files can be read in CHARMM, AMBER, and GROMACS formats. Non-orthogonal periodic cells may be used for constant pressure and temperature simulations. Free energy perturbation and a variety of steering methods are supported. Interactive steering has been completely redesigned to reduce latency and other usability limitations.

- NAMD is more flexible and easier to use. The Tcl scripting language can now be used by end-users to modify the program. A new tool, psfgen, has eliminated the need for other packages when building simulation input files. The program is also simpler to run, particularly on serial machines.

- NAMD serial performance and parallel scalability have dramatically improved. The implementation, tuning, and parallelization of the particle-mesh Ewald algorithm has enabled production runs of biomolecular interest with full electrostatics on up to 512 processors. Load balancing improvements have demonstrated scaling of cutoff calculations to 2048 processors. Minimization has been reimplemented with adaptive conjugate gradients, a substantial improvement over the previous quenching method.

- NAMD 2.4 release with AMBER file compatibility (parm and coordinate input only). The new psfgen tool for building PSF structure files. Simpler to run on a single workstation. (No more rsh!) New ports to the Compaq AlphaServer SC, Scyld Beowulf, and Mac OS X. Improved serial performance, particularly with PME on Alpha.

- NAMD 2.5b1 release with improved constant pressure simulation and coordinate wrapping. Additional parameters can be changed during a simulation script. Fixes to AMBER parm file reader for AMBER 7 or large molecules.

- NAMD has been ported to all desktop and major massively parallel platforms, including Windows, Mac OS X, Linux and Unix workstations, Cray T3E, Origin 2000, IBM SP, and the new Alpha, IA32, and IA64 terascale platforms at PSC and SDSC. Source code is available via the web or CVS. Precompiled binaries are distributed for all standard platforms for the convenience of our users.

  There are currently 50 external users with access to the NAMD CVS tree.

A literature search of NAMD citations over the past year yielded the following results:

Izaguirre, J.A., Catarello, D.P., Wozniak, J.M., Skeel, R.D., "Langevin stabilization of molecular dynamics," J. Chem. Phys. 114, 2090-2098 (2001).

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Krammer, A., Craig, D., Thomas, W.E., Schulten, K., Vogel, V., "A structural model for force regulated integrin binding to fibronectin's RGD-synergy site," Matrix Biol. 21, 139-147 (2002).

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Recent NAMD talks and tutorials are listed in the Dissemination and the Training sections, however it should be noted that NAMD, with the talk "Scalable Molecular Dynamics for Large Biomolecular Systems," was one of the three finalists for the prestigious Gordon Bell Award at the SC 2000 (formerly Supercomputing) conference.

The Department of Energy's National Energy Research Scientific Computing Center (NERSC) has selected NAMD as a vendor benchmark for their next procurement. NERSC currently operates a 2528 processor, 3.8 teraflop IBM SP, the most powerful unclassified supercomputer in the world at the time of writing.

VMD In the past year, starting May 2001 there were nearly 100,000 visitors to the VMD web pages. Recent VMD accomplishments include:

- VMD 1.7.1
  - Volumetric data loading via the scripting interface
  - Isosurface and volume slice display, used to visualized electron density maps, potential maps, electron orbitals and other spatially enumerated data
  - Scanline interleaved stereoscopic rendering supporting inexpensive PC stereo glasses, such the Eye3D glasses.
  - First implementation of VMD plugin exentions
  - Inclusion of the 'psfgen' structure building package and the 'solvate' package as VMD plugin extensions
  - Built-in support for WireGL-based rendering on tiled display and cluster-based visualization systems
  - Improved scene export to Tachyon, Raster3D, and POV-Ray renderers.
  - Faster secondary structure determination with a modified version of the Stride program.
- VMD 1.7.2
  - Improved the user interface with the mouse and the VMD graphics window, specifically for the Windows platform.
- Version independent improvements (plugin components, BioCoRE integration)

  - Greatly improved VMD/BioCoRE publish/sync functionality, supporting both Unix and Windows, with a saved session selection window.
  - New VMD movie maker plugin, provides a completely automated movie generation feature that researchers can use to create MPEG, AVI, and Quicktime movies of molecular dynamics trajectories and structure rotation visualizations. Works with all recent versions of VMD.
  - Updated the psfgen plugin with several improvements to the scripting interface.
  - Implemented a scripting control mechanism by which VMD sessions can be driven from web pages. This feature allows complex web-based tutorials to be developed combining web-based materials with interactive VMD visualization and analysis sessions, and most recently with the new psfgen structure building features.

  VMD is now available on all major computer platforms.

There are currently 66 external users with access to the VMD CVS tree.

VMD demonstrations offered in the past five years:

- 341 VMD demonstrations given at the Resource projection facility
- 248 VMD CAVE demonstrations given at NCSA

In the past year, 10 VMD demonstrations were offered off-site by non-Resource members.

VMD talks, tutorials, and workshops presented:

- October 2001, Center for Parallel Computers, Royal Institute of Technology, Sweden, 2001 CAVE Programming Workshop, Scientific visualization session, Invited talk and tutorial, *Biomolecular Visualization*
- August 2001, Los Angeles, California, ACM SIGGRAPH 2001 Annual Conference, Demonstration, *Biomolecular Simulation and Visualization*
- March 2001, Research Triangle Park, North Carolina, ACM SIGGRAPH 2001 Symposium on Interactive 3D Graphics, *A System for Interactive Molecular Dynamics Simulation*
- April 2000, University of Notre Dame, *VMD - High Performance Molecular Visualization*
- April 2000, University of Missouri-Rolla, *VMD - High Performance Molecular Visualization*

- November 1998, University of Missouri-Rolla, *VMD - A Molecular Visualization System*

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BioCoRE In the past year there were 9,852 visitors to the BioCoRE web pages. Recent BioCoRE accomplishments include:

- Server software release (March 2002)
- Simulation submission at supercomputer sites
  - Monitor all of your jobs from one web page
  - Support for newest machines at PSC, NCSA, Resource
  - Support for Globus jobs
  - Run any program installed on remote machine
  - Additional support for NAMD

  - File uploading for supercomputer jobs
- NAMD configuration file generator
  - Context-sensitive help
  - Error prevention
- Control panel: Instant messenger, instant notifier
- Web site library / Project-wide bookmarks file
- VMD publish/synchronize
- Thumbnail images for published VMD states
- Integrated file system
  - All project files accessible from one place
  - JMV applet integration

BioCoRE, a web-based environment, is platform-independent. Since it is a purely web-based program, the release mechanism is different than that of traditional programs such as VMD/NAMD, and merely requires access to the BioCoRE web site. Thus, handling BioCoRE updates is extremely flexible and updates to the code are released weekly.

The BioCoRE server software was released on the web in early 2002, offering researchers the option of running their own BioCoRE server. Thus, in addition to the Resource's server, BioCoRE servers are available now in the UIUC Department of Chemistry, and will soon be running at NCSA and PSC. Additional installations are being discussed with industry, academic and federal institutions across the US and overseas.

Last but not least, BioCoRE will be expanded to include training tools which will become a major component and mission of this collaborative environment.

The following BioCoRE demonstrations were given in the past funding period:

- November 1999: SuperComputing 99 Conference, Portland, Oregon.
  `http://www.ks.uiuc.edu/Research/biocore/presentations/sc99.shtml`
- May 1, 2000: HICS Conference, Beckman Institute, *Demonstration of BioCoRE/Haptic*
  `http://www.ks.uiuc.edu/Research/biocore/presentations/HICS_2000/`
  (20 visitors)
- May 11, 2000: BioCoRE Demonstration, Beckman Institute (Olaf Kuebler, President, ETH Zurich; Thomas Eichenberger, Assistant to the President; Computer Science Professors: Moira Norrie, Peter Windmayer, Walter Gander)

- July 17, 2000: BioCoRE Demonstration, Beckman Institute (Ernest Retzel, Director of the Computational Biology Centers, U of Minnesota)
- March 2,3 2001: 2001 College of Engineering Open House, *BioCoRE Demonstration* `http://www.ks.uiuc.edu/Research/biocore/presentations/COEOpenHouse2001/` (120 visitors)
- March 22, 2001: BioCoRE Demonstration, Beckman Institute (Scyld Computing Corporation staff)
- April 6, 2001: BioCoRE Job Submission/Monitoring demonstration, Beckman Institute (NCSA visitors)
- November 29, 2001: BioCoRE demonstration (Director Pierre Wiltzius, Beckman Institute, Dean David Daniel, College of Engineering, Director John Parks, Research Park and Incubator)
- April 15, 2002: BioCoRE demonstration (Vijay Pande, Stanford University, Nicolae-Viorel Buchete, Boston University)
- April 15, 2002: BioCoRE demonstration and discussion (Ferenc Molnar, BASF Germany)

BioCoRE talks and posters given in the past funding period include:

- April 27, 2000: *BioCoRE: A Collaboratory for Structural Biology*, Imaging Technology Group Forum, Beckman Institute.
- October 27-29, 2000: NCRR Biomedical Collaboratories Workshop Pittsburgh Supercomputer Center.
- November 15, 2001: BioCoRE - Submits, Runs and Visualizes your Simulation from Afar, 2001 SC Global event. (Access Grid presentation)
- February 23-27, 2002: BioCoRE: A Biological Collaborative Research Environment, 2002 Biophysical Society Meeting (Poster)
- May 8, 2002: BioCoRE: A Biological Collaborative Research Environment, 2002 National Computational Science Alliance All-Hands Meeting (Poster)

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.

The last software evaluation surveys we conducted for VMD and NAMD were in Aug. 2000 and for BioCoRE in Jan. 2002.

An overwhelming majority of VMD users are affiliated with academic institutions (81%) and use VMD for research (72%). 15% of VMD respondents reported to be funded by NIH. 45% of VMD users run the program on a Windows machine. VMD meet the expectations of 92% of VMD respondents, VMD-support meet the expectations of 96% of VMD respondents, 96% reported that VMD web pages are instructive and 94% are satisfied overall.

An overwhelming majority of NAMD users are affiliated with academic institutions (80%) and use NAMD for research (80%). 11% of the respondents reported to be funded by NIH. 65% of NAMD users run the program on Linux-i686 . NAMD meet the expectations of 89% of NAMD respondents, NAMD-support meet the expectations of 98% of NAMD respondents, 94% reported that NAMD web pages are instructive and 96% are satisfied overall.

An overwhelming majority of BioCoRE users are affiliated with academic institutions (93%) and use BioCoRE for research (90%). 60% of the respondents reported to be funded by NIH. BioCoRE members find the environment easy to learn (80%) and easy to use (72%). BioCoRE-support meets the expectations of 86% of respondents, 57% of whom reported satisfaction with their work within BioCoRE, and 66% are satisfied overall. The results are promising and indicate a positive reception and future success for the program.

Lending out Expertise

Additional service activities the Resource engages in are:

- User support
- Collaborations
- Visitor Program

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 quality of our products. Our user population keeps growing and consequently we are expected to invest more and more resources in user support. With over 20,000 users across our technology area, support is a major task, and we take it very seriously. Only recently we revisited our support policies and adjusted them to both the growing demand and the growing number of software products we develop and maintain. The guidelines call for the programmers to respond to all support inquiries within 24 hours of receipt or next business day. Nontrivial inquiries may take longer, preferably no longer than three business days.

We supply assistance to biomedical researchers who would benefit from the use of our Resource's expertise for their research. In addition to the clear service value of the collaborations reported earlier, in the past five years over 30 visitors have stayed with us and received on-site training with high performance computational tools. The visitors typically fund their visit here, and we supply the computing resources and knowledge. These visits are beneficial to all involved, and more details on the individual visitors are included in the Training section.

Seminars 1997-2002 In the past five years we have organized and hosted over 110 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 Beckman 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 at `http://www.ks.uiuc.edu/Services/Seminar/` for easy information retrieval. Below is the complete list of the Resource seminars in the past year:

August 31, 2001, Massimo Olivucci, Dipartimento di Chmica, Universit di Siena, Siena, Italy, *The Structure of the Photoisomerization Path for the Rhodopsin Protein Retinal Chromophore*

August 31, 2001, Iwao Ohmine, Chemistry Department, Nagoya University, Japan, *Water Dynamics; Fluctuation and Chemical Reactions*

October 1, 2001, Robert Birge, University of Connecticut, Storrs, CT, *Protein-Based Three-dimensional Memories and Associative Processors*

October 1, 2001, Shaul Mukamel, University of Rochester, Rochester, NY, *Collective Electronic Excitations and Coherence Sizes in Dendrimers and Photosynthetic Antennae*

October 18, 2001, Willy Wriggers, The Scripps Research Institute, La Jolla, CA, *Reconciling Shape with Structure: Strategies for Multi-Resolution Fitting of Biophysical Data*

October 22, 2001, Catherine Royer, Center de Biochimie Structurale, Universite Montpellier, France, *Volume Changes, Packing and Hydration: Insights into Protein Folding from High Pressure Studies*

October 29, 2001, Peter Nollert, University of California San Francisco, San Francisco, CA, *Structure of a Glycerol and Water Conducting Channel and the Basis for its Selectivity*

November 12, 2001, Sunny Xie, Harvard University, *Single Molecule Enzymatic and Conformational Dynamics*

November 19, 2001, Chris Johnson, University of Utah, *BioPSE: A Biomedical Problem Solving Environment*

December 3, 2001, Jiali Gao, University of Minnesota, *Combined QM/MM simulations: From Opsin Shifts to Enzymatic Reactions*

January 28, 2002, John Straub, Boston University, Boston, MA, *Structure, Dynamics and Activity of the Alzheimer's Ab-peptide*

February 11, 2002, Herbert Edelsbrunner, Duke University, Durham, NC, *Bio-Geometric Modeling*

February 18, 2002, Bing Jap, Lawrence Berkeley National Lab, Berkeley, CA, *Molecular Basis for the Water-specific Transport Mechanisms of AQP1 Water Channel*

March 11, 2002, Oliver Kuehn, Freie Universitaet Berlin, Germany, *Ultrafast Dissipative Excitation Energy Transfer Dynamics in Light-harvesting Antenna Complexes*

March 25, 2002, Deborah Leckband, University of Illinois at Urbana-Champaign, IL, *Novel Mechanisms in Biological Adhesion*

April 1, 2002, Tobin Sosnick, University of Chicago, Chicago, IL, *Kinetics of H-Bond Formation in Protein Folding*

April 15, 2002, Vijay Pande, Stanford University, Stanford, CA, *Folding@Home: Atomistic Simulations of Protein Folding on the Hundreds of Microsecond Timescale using Worldwide Distributed Computing*

April 15, 2002, Ferenc Molnar, BASF AG, Ludwigshafen, Germany, *Molecular Modeling and Polymer Research at BASF – Informal Seminar*

April 22, 2002, Robert Laughlin, Stanford University, Stanford, CA, *Balanced Branching in Transcription Termination*

June 13, 2002, Wolfgang Junge, Division of Biophysics, University of Osnabrueck, Germany, *ATP Synthase: Elastic Power Transmission Between Two Rotary Stepper Motors*

Service efforts in earlier years of the funding cycle yielded the following highlights:

- The Resource organized an internal retreat for all the regular Resource members (May 13–14, 2001) at Eagle Creek Retreat, about an hour away from Champaign-Urbana. The meetings offered an ideal setting and a relaxed atmosphere for deep discussions and the exchange of ideas between the members about present and future research and development efforts at the Resource.

- The Resource organized a meeting held on April 16–17, 2000 at the Beckman Institute, UIUC, entitled "Parallel MD Development and Use— Challenges and Opportunities".** The conference was sponsored by the NIH/NCRR, and offered a forum for researchers and developers who employ parallel computers in molecular modeling to exchange ideas on programming strategies, and to demonstrate what can be achieved in simulations today. The participants focussed on the state-of-the-art in parallel computing for molecular dynamics.

- The Resource participated on March 3–4, 2000, in the Beckman Institute's open house in conjunction with the UIUC College of Engineering. The Resource presented a demonstration titled "BioCoRE and 3D Interactive Molecular Dynamics". The 294 visitors, students, faculty, and others showed a great interest in the work and expressed immense respect and appreciation.

- The Resource organized a meeting held on March, 3–4, 1999 in Rockville, MD, entitled Opportunities in Molecular Biomedicine in the Era of Teraflop Computing. The conference was sponsored by the NIH/NCRR, and addressed the explosive growth in computational power and biological databases, and their expected impact on the future of biomedical research. Twenty leading scientists in the field of computational structural biology were invited to discuss relevant research opportunities that will arise with the anticipated increase of computer power, and to elucidate how a state-of-the-art computer facility dedicated to biomedical sciences could facilitate such opportunities. About 50 observers from academic institutions, federal agencies and industry attended the talks and participated in the discussions.

- At the 1999 Beckman Institute Open House more than 190 visitors came to the VMD demonstrations, which were presented in the 3D visualization facility at the Resource on March 5–6, 1999. The VMD demonstration was voted "Overall Best" by the visitors to the Beckman event.

- The Resource has held its own Open House on December 3, 1998. The event attracts many on-campus visitors, both students and faculty, and leads to renewed and increased interest in our research and development efforts. More than 100 visitors joined us for tours of the facility and 3D demonstrations.

**`http://www.ks.uiuc.edu/Services/Meetings_Tutorials/Meetings/ParallelMD/`

- In 1998 we created the first VMD CD, which was widely distributed.
- The Resource organized an internal retreat for all the regular Resource members (March 13–14, 1998) at Allerton Park, just outside of Champaign–Urbana. The meetings offered an ideal setting and a relaxed atmosphere for deep discussions and the exchange of research and development ideas between members.

TRAINING

The Resource recognizes the vital importance of training for the education and professional growth of young scientists. While in the past ffive years the Resource has focused more on conventional training opportunities, in the future the Resource will expand its web utilization and establish a wide selection of web-based training venues that would reach a larger audience and would enable a broader coverage of contemporary and relevant biomedical areas than before.

In the past funding cycle we have significantly increased the scope and nature of our training efforts and offered a variety of opportunities using a range of tools and media:

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

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 forum, Biological Physics 001, offered in Spring 2001, was organized by K. Schulten and dealt with the key role of life sciences in the future world of science and technology. The well-attended series of talks, which attracted a diverse cross-section of the UIUC campus, explained questions, concepts, and challenges in the field to non-biologists. Our faculty also participates in summer school initiatives bridging physical and life sciences. T. Martínez offered a class at the NSF-funded Summer School on Computational Materials Science in Summer 2001. We make our resources available to regular UIUC classes several times a year, and to rotation students from various departments.

Tutorials In the past year several off-site NAMD tutorials were offered at NCSA, PSC ands other locations. Through our collaboratory environment, BioCoRE, distant tutorials were offered in Germany (Heidelberg) and Australia. Students in both locations logged into the BioCoRE server located in Urbana, IL, and ran their projects across the Atlantic and the Pacific Oceans respectively, taking advantage of the Resource's computational power. 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 at `http://www.ks.uiuc.edu/Services/Meetings_Tutorials/Tutorials/`. Recent Resource tutorials include:

- NAMD Workshop at NCSA and on the Access Grid, April 17-19, 2002
- Beckman Open House 2002, March 8-9, 2002
- VMD Web-based presentation tutorial, January 16, 2002
- NAMD and VMD at SC2001, November 12-15, 2001
- BioCoRE at SC2001, November 15, 2001
- NAMD Molecular Dynamics Workshop at PSC, August 15-18, 2001
- VMD with NAMD, JMV, and BioCoRE at SIGGraph 2001, August 14th through 16th, 2001
- NAMD Linux Cluster Tutorial:
  - June 19, 2001
  - June 26, 2001 - NCSA Linux Revolution Conference
  - July 13, 2001
- Development Tools Tutorial, April 3rd, 2001
- BioCoRE Tour
- BioCoRE Job Submission Tutorials (Heidelberg 2000; Perth 2000; Pittsburgh 2001)
- VMD-1.6 Tutorial
- VMD-1.5 Tutorial
- VMD-1.3 and 1.4 Tutorial
- NAMD Tutorial
- "Linux Clusters" talk (PDF), ITG Forum, November 11 1999

Internal tutorials featured a recent session 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.

Resource Library In the past four years, we have purchased over 400 new books that expand our well stocked Resource library. We continue to subscribe to the following journals:

- Biophysical Journal
- C++ Report
- Chronicle of Higher Education
- Dr. Dobb's Journal
- Journal of NIH Research
- Linux Journal
- MacWorld
- Nature
- Nature Structural Biology
- Physics Today
- Science
- Structure with Folding and Design
- SysAdmin
- Trends in Biochemical Sciences
- Windows Developer's Journal

The journals offer the latest information on research and development areas relevant to the Resource activities.

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

PhD Recipients

1. C. Koretke
   Ph.D. in Chemistry, University of Illinois, 1997

2. Willy Wriggers
   Ph.D. in Physics, University of Illinois, 1997

3. Michael Zeller
   Ph.D. in Physics, University of Frankfurt 1997

4. Ilya Logunov
   Ph. D., Chemistry, University of Illinois, 1998

5. Sergei Izrailev
   Ph. D., Physics, University of Illinois, 1998

6. Dorina Kosztin
   Ph. D., Chemistry, University of Illinois, 1998

7. Jesus Izaguirre
   Ph.D., Computer Science, University Of Illinois, Summer, 1999

8. Hui Lu
   Ph.D., Nuclear Engineering, University Of Illinois, Fall 1999

9. Ana Damjanovic
   Ph.D., Physics, University Of Illinois, Spring 2001

10. Thorsten Ritz
    Ph.D. in Physics, University of Ulm, Germany, Feb 2001

MA/MSc Recipients

1. Krishnan Varadarajan
   M.S. in Computer Science, University of Illinois, 1999

2. Parthasarathy Ramachandran
   M.S. in Computer Science, University of Illinois, 1999

3. Ismail Tezcan
   M.S. in Computer Science, University of Illinois, Spring 2002

Postdoctoral Associates

1. Attila Gursoy
2. Ivo Hofacker
3. Sergey Stepaniants
4. Xiche Hu
5. Ferenc Molnar
6. Christian Forst
7. Margit Mollhoff
8. Dorina Kosztin
9. Jerome Baudry

Undergraduate Trainees

1. Jiayang Ruan (Fall 97)
2. Vera Koffman (Spring 97 - Spring 98)
3. John Lin (Spring 97)
4. Jennifer Phend, REU (Summer 97)
5. David Koffman, REU (Summer 97)
6. Jonathan Marks (Summer 98)
7. Adrienne Shapiro (Summer 98)
8. Nicholas Dietz (Summer 98)
9. Salih Adem (Summer 98)
10. Amit Mehta (Summer 99)
11. Paul Grayson (Summer 99)
12. Justin Wozniak (1998-2000)
13. Gary Tedeschi (Summer 2000)

Visitors In the past five years the Resource implemented a visitor program and hosted young scientists for periods ranging from one week to several months. 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 the Resource members, and bring back to their home laboratories critical new skills and 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. The visitors in the past five years were:

1. Morten Jensen, Department of Chemistry, Technical Univ. of Denmark (Spring, 2002)
2. Nicolae-Viorel Buchete, Chemistry Department, Boston University (April 2002)
3. Carsten Tietz, Physical Institute, Universitaet Stuttgart (Spring 2002)
4. Andrew Aird, Physical Institute, Universitaet Stuttgart (Spring 2002)
5. Grischa Meyer, Physics, U West Australia (January-February, 2002)
6. David Craig, U of Washington (November 2001)
7. Ulrich Kleinekathoefer, Institute of Physics, Chemitz Univ. of Technology, Chemitz, Germany (Summer 2001)
8. Felix Autenrieth, University of Stuttgart, Germany (Summer and Fall 2001)
9. Jan Saam, Humboldt University Berlin, Germany (Summer and Fall 2001)
10. Morten Jensen, Department of Chemistry, Technical University of Denmark (Spring and Summer, 2001)
11. Michael Patra, Institute Lorentz, Leiden, Netherlands (November 2000)
12. Jian Sun, Physiology/Biophysics, Mount Sinai School of Medicine (September 2000)
13. Nick Wright, UC Irvine - Chemistry (Summer 2000)
14. Stephen Birmanns, Zentralinstitut fuer Angewandte Mathematik, Juelich, Germany (Summer 2000)
15. Gary Tedeschi, REU, Biophysics, UCSD (Summer 2000)
16. Professor Robijn Bruinsma, UCLA (Winter 2000)

17. Felix Autenrieth, University of Stuttgart, Germany (Summer and Fall 99)
18. Paul Grayson, REU, Physics, MIT (Summer 99)
19. Amit Mehta, REU, Physics, Cornell, (Summer 99)
20. Dr. Emadeddin Tajkhorshid, German Cancer Research Center, Heidelberg University (Summer 99)
21. David Craig, University of Washington (Summer 99)
22. Professor Attila Gursoy, Bilkent University, Ankara, Turkey (Summer 99)
23. Dr. Emadeddin Tajkhorshid, German Cancer Research Center, Heidelberg University (Fall 98)
24. Salih Adem, Bilkent University, Physics Department, Ankara, Turkey (Summer 98)
25. Felix Autenrieth, University Stuttgart, Germany (Summer 98)
26. David Hurwitz, Department of Chemistry, University of North Carolina (Spring 98)
27. Andre Krammer, University of Seattle (Spring 98)
28. Professor Zhirong Sun, Qing Hua University, Beijing, China (Spring 98)
29. Andre Krammer, University of Seattle (Summer 97)
30. David Koffman, REU (Summer 97)
31. Jennifer Phend, REU (Summer 97)

Manuals and Tours Our software manuals have been available on the web for many years, and are regularly updated. BioCoRE has been experimenting with a new training concept which combines an online tutorial with a slide tour. The 'tour' is regularly updated and developed.

Finally, Training efforts in earlier years of the past funding cycle yielded the following highlights:

- The Resource organized an internal summer school for six new graduate students who joined the Resource in the Summer of 1999.
- The Resource organized internal tutorials for members to improve their computational know-how, writing skills, and involvement with proposal preparation.

DISSEMINATION

The Resource's dissemination and outreach efforts have greatly intensified in the past funding cycle, 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.

The Resource produced brochures and videos, and was also featured for its accomplishments in trade magazines and other printed and online media, for example reviews of VMD in *BioMedNet* (Sep 2001) and *CAD Report* from SIGGRAPH 2001 (Sep 2001). The Resource made the covers of prestigious publications (most notably in *Biophysical Journal*, *Journal of Physical Chemistry*, *Physics Today*, *Proteins*, and others) as well as books (URL: `http://www.ks.uiuc.edu/Publications/Covers/`). Resource personnel presented talks and posters in professional meetings.

The Resource appeared in stories in popular media, including in the *Chronicle of Higher Education*, *Dallas Morning News*, *The News Gazette* (Champaign, IL), Supercomputer Center magazines and reports and more. All these news-making stories are posted on the Resource web site in the "In the News" section at
`http://www.ks.uiuc.edu/Publications/stories.shtml`:

- April 22 2002 - Researchers Explain How Proteins Filter Water into Cells
- April 18 2002 - Scientists Document Water Molecule Movement Across Cell Walls
- Oct 20 2001 - US Health and Human Service (HHS) Secretary Tommy Thompson's visit
- Oct 18 2001 - NCSA's First Itanium Linux Cluster Shows Top Performance in Test Runs
- Oct 4 2001 - Public Computing on a Super Scale
- Sep 14 2001 - BioMedNet review of VMD 1.7
- Sep 10 2001 - The Road to La-La Land
- May 1 2001 - Proteins are vastly more complicated than previously realized
- January 29 2001 - University of Illinois's Theoretical Biophysics Group Using Scyld Beowulf Operating System on new Super Computer
- Dec 6 2000 - VMD: a graphical tool for the modern chemists

- Nov 10 2000 - Molecular Visualization for the Masses - VMD mentioned in BioMedNet article
- July 10 2000 - The Right Direction - Data revealing how magnetism guides animals
- June 28 2000 - Researchers Turn to Computer Models to Learn What Experiments Can't Teach
- June 28 2000 - A Guided Tour of Steered Molecular Computing
- June 27 2000 - The Rude Mechanicals
- June 22 2000 - Migrating Birds May 'See' Magnetic Field
- March 28 2000 - People Harvest Technology
- March 15 2000 - Wie Zugvgel das Magnetfeld der Erde sehen knnen
- March 3 2000 - Animals and the Earth's Magnetic Field

The Resource has scheduled a BioCoRE technical presentation and demonstration on using the AccessGrid as part of SC2001 and presented a poster at the May 2002 Alliance All-hands meeting. The Resource web site was selected by ISI (Institute for Scientific Information) for Current Web Contents.

Publications

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

- 147 refereed articles (see below)
- 300 talks (PIs and other members as specified below)
- 60 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: (T)

TOTAL RESULTING PUBLICATIONS 1997-2002:
Books: 1 Papers: 83

Total for the last year (2001-2002):

PUBLISHED:

Books: 0 Papers: 5

IN PRESS OR SUBMITTED:

Books: 0 Papers: 7

Papers (2001-2002)

PUBLISHED:

- 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.
- M. Bhandarkar, L. V. Kale, E. de Sturler, and J. Hoeflinger. *Object-Based Adaptive Load Balancing for MPI Programs.* Accepted for publication at the International Conference on Computational Science, May 2001.
- R. Brunner, J. Phillips and L. V. Kale. *Scalable Molecular Dynamics for Large Biomolecular Systems.* (Finalist for Gordon Bell Award) Proceedings of SC2000 CD-ROM, Dallas, 2002.
- N. Saboo, A. Singla, J. Unger, and L. V. Kale. *An emulator for blue gene class machines.* In Proceedings of the workshop on massively parallel computing, IPDPS-2001 (San Fransisco, CA).
- M. Sener and K. Schulten. *A general random matrix approach to account for the effect of static disorder on the spectral properties of light harvesting systems.* Physical Review E, 65:031916, 2002. (12 pages).

IN PRESS OR SUBMITTED:

- M. Ben-Nun and T. J. Martinez. *Ab Initio Quantum Molecular Dynamics.* Invited article for Adv. Chem. Phys. In Press.

- K. Frimand, T.J. Martinez and K. Jalkanen. *SCC-TB, DFT/B3LYP, MP2, AM1, PM3 and RHF study of ethylene oxide and propylene oxide structures, VA and VCD spectra.* Chemical Physics, In press, 2002.

- Q. Ma, J. Izaguirre, and R.D. Skeel. *Verlet-I/r-RESPA is limited by nonlinear instability.* SIAM J. Sci. Comput., Submitted, 2002.

- J. Quenneville, M. Ben-Nun, and T. J. Martinez. *Photochemistry from First Principles: Advances and Future Prospects.* J. Photochem. Photobiol. In Press, 2001.

- R. D. Skeel and D. J. Hardy. *Practical Construction of Modified Hamiltonians.* SIAM J. Sci. Comput., 2001, In Press.

- R.D. Skeel, I. Tezcan, and D.J. Hardy. *Multiple grid methods for classical molecular dynamics.* J. Comput. Chem., In press. 2002

- A. Toniolo, M. Ben-Nun, and T. J. Martnez. *Optimization of Conical Intersections with Floating Occupation Semiempirical Configuration Interaction Wavefunctions.* J. Phys. Chem., In press, 2002.

BTA unit: (C)

TOTAL RESULTING PUBLICATIONS 1997-2002:
Books: 0 Papers: 41

Total for the last year (2001-2002):

PUBLISHED:

Books: 0 Papers: 8

IN PRESS OR SUBMITTED:

Books: 0 Papers: 6

Papers (2001-2002)

PUBLISHED:

- S. Hayashi, E. Tajkhorshid, E. Pebay-Peyroula, A. Royant, E. M. Landau, J. Navarro, and K. Schulten. *Structural determinants of spectral tuning in retinal proteins - bacteriorhodopsin vs sensory rhodopsin II.* Journal of Physical Chemistry B, 105:10124-10131, 2001.

- M. Jensen, E. Tajkhorshid, and K. Schulten. *The mechanism of glycerol conduction in aquaglyceroporins.* Structure, 9:1083-1093, 2001.
- A. Krammer, D. Craig, W. E. Thomas, K. Schulten, and V. Vogel. *A structural model for force regulated integrin binding to fibronectin's RGD-synergy site.* Matrix Biology, 21:139-147, 2002.
- T. W. Lynch, D. Kosztin, M. A. McLean, K. Schulten, and S. G. Sligar. *Dissecting the molecular origins of protein-nucleic acid recognition: Hydrostatic pressure and molecular dynamics.* Biophysical Journal, 82:93-98, 2002.
- T. W. Lynch, M. A. McLean, D. Kosztin, K. Schulten, and S. G. Sligar. *High pressure gel mobility shift analysis and molecular dynamics: Investigating specific protein-nucleic acid recognition.* In R. Hayashi, editor, Trends in High Pressure Bioscience and Biotechnology, pages 87-94. Elsevier, 2002.
- R. Phillips, M. Dittrich, and K. Schulten. *Quasicontinuum representations of atomic-scale mechanics: From proteins to dislocations.* Annual Review of Materials Research, 32, 2002.
- E. Tajkhorshid, P. Nollert, M. 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.
- F. Zhu, E. Tajkhorshid, and K. Schulten. *Molecular dynamics study of aquaporin-1 water channel in a lipid bilayer.* FEBS Letters, 504:212-218, 2001.

IN PRESS OR SUBMITTED:

- R. Braun, M. Sarikaya, and K. Schulten. *Genetically engineered gold-binding polypeptides: Structure prediction and molecular dynamics.* Journal of Biomaterials Science, 2002. In press.
- J. Ervin, E. Larios, S. Osvath, K. Schulten, and M. Gruebele. *Hyperfluorescence: due to a folding intermediate or to a conformationally flexible native state* Biophysical Journal, 2002. In press.
- S. Hayashi, E. Tajkhorshid, and K. Schulten. *Structural changes during the formation of early intermediates in the bacteriorhodopsin photocycle.* Biophysical Journal, 2002. In press.
- M. Jensen, S. Park, E. Tajkhorshid, and K. Schulten. *Energetics of glycerol conduction through aquaglyceroporin GlpF.* Proceedings of the National Academy of Sciences, USA, 2002. In press.

- M. 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, Submitted, 2002.

- F. Zhu, E. Tajkhorshid, and K. Schulten. *Pressure-induced water transport in membrane channels studied by molecular dynamics.* Biophysical Journal, 83, 2002. In press.

BTA unit: (D)

TOTAL RESULTING PUBLICATIONS 1997-2002:
Books: 0 Papers: 10

Total for the last year (2001-2002):

PUBLISHED:

Books: 0 Papers: 6

IN PRESS OR SUBMITTED:

Books: 0 Papers: 0

Papers (2001-2002)

PUBLISHED:

- A. Damjanovic, I. Kosztin, U. Kleinekathoefer, and K. Schulten. *Excitons in a photosynthetic light-harvesting system: A combined molecular dynamics, quantum chemistry and polaron model study.* Physical Review E, 65:031919, 2002. (24 pages).

- M. Gao, H. Lu, and K. Schulten. *Simulated refolding of stretched titin immunoglobulin domains.* Biophysical Journal, 81:2268-2277, 2001.

- X. Hu, T. Ritz, A. Damjanovic, F. Autenrieth, and K. Schulten. *Photosynthetic apparatus of purple bacteria.* Quarterly Reviews of Biophysics, 35:1-62, 2002.

- I. Kosztin, R. Bruinsma, P. O'Lague, and K. Schulten. *Mechanical force generation by G-proteins.* Proceedings of the National Academy of Sciences, USA, 99:3575-3580, 2002.

- T. Ritz, A. Damjanovic, and K. Schulten. *The quantum physics of photosynthesis.* ChemPhysChem, 3:243-248, 2002.

- T. Ritz, S. Park, and K. Schulten. *Kinetics of excitation migration and trapping in the photosynthetic unit of purple bacteria*. Journal of Physical Chemistry B, 105:8259-8267, 2001.

IN PRESS OR SUBMITTED:

None.

Talks

The Resource PIs gave the following talks in the last year of the funding cycle:

Laxmikant Kale

- April 25-28 2002, International Parallel and Distributed Processing Symposium, San Francisco, CA.

Robert Skeel

- March 17-21 2002, University of Illinois, Urbana, IL. From La Jolla, CA (on sabbatical) to check on status of research.
- July 26-August 3, 2001, International Conference on Scientific Computation and Differential Equations, Vancouver, Canada.
- August 11-19 2001, Siggraph 2001, Los Angeles, CA.

Klaus Schulten

- July 25-27 2001, Nagoya, Japan. *Static and Dynamic Disorder of the Exciton System in Light Harvesting Complexes LH2 of Purple Bacteria*
- July 28-August 5 2001, 4th International conference on Biological Physics, Kyoto, Japan. *Observation and Multiscale Modeling of Bio-molecular Mechanics: How Proteins Pull and DNA Coils*
- August 12-14 2001, Center for Nonlinear Studies Workshop, Los Alamos, NM. *Excitons in a Photosynthetic Light-Harvesting System: A Combined Molecular Dynamics/Quantum Chemistry, Polaron Model, and Random Matrix Study*
- August 15-16 2001, Pittsburgh Supercomputing Center Workshop, Pittsburgh, PA. Lecture 1: *Intro to Molecular Dynamics Simulations* Lecture 2: *What Can we Learn From MD?* Lecture 3: *Case Study: Protein Membrane Simulations*

- August 20 2001, CalTech, San Diego, CA. Visit with collaborator Rob Phillips
- September 10-11 2001, NSF Workshop on Computational Physics Arlington, VA. *Concepts and Methods in Computational Bioelectronics*
- October 2-7 2001, International Center for Theoretical Physics, Trieste, Italy. Lecture 1: *Membrane Proteins: A Tale of Conduction* Lecture 2: *Membrane Proteins: A Tale of Harvesting* Lecture 3: *Membrane Proteins: A Tale of Vision*
- October 19-November 4 2001, University of Western Australia, Perth, Australia. Lecture 1: *The Mechanism of Water and Glycerol Conduction in Aquaglyceroporins* Lecture 2: *The Innate (310K) Thermal Disorder in Bioelectronic Systems as Revealed in Photosynthesis* Summer School at Perth - Lecture 1: *Water transport in kidneys and molecular modeling* Lecture 2: *Muscle elasticity and atomic force microscopy* Lecture 3: *Regulation of the genome and mechanical engineering* Lecture 4: *Harvessting sun light and quantum physics* Lecture 5: *Photosynthesis and solar technology* Lecture 6: *Vision and ultrafast chemistry* Lecture 7: *Neural pulses and non-linear dynamics* Lecture 8: *Pictures in the brain and mathematics* Lecture 9: *Slime mold amoebae and pattern formation* Lecture 10: *Bird navigation and spin chemistry*
- November 7-9 2001, Florida State University, Tallahassee, FL.
- December 4-10 2001, Swiss Biochemical Society Meeting, Lausanne, Switzerland. *Bioinformatics and Proteomics: From Sequence to Function*
- January 8-10 2002, PMMB Meeting – Modeling Across the Scales – Atoms to Organisms, Santa Fe, NM, *Modeling the Mechanical Functions of Proteins and DNA*
- January 14 2002, ICAM – Workshop on Self-Organizing Biomolecules: the Evolving Picture, Santa Fe, NM. *Studying Water and Glycerol Transport in the Membrane Channel Protein Aquaglyceroporin*
- January 19-26 2002, Winter Seminar, Klosters, Switzerland. Lecture: *The Mystery of Membrane channels, Fast Conduction, and Strong Selection, Approached Through Crystallography and Modelling*
- February 8 2002, Iowa State University, Ames, IA. *Static and Dynamic Disorder of the Exciton System in Light Harvesting Complexes LH2 and PS1*
- February 23-27 2002, Biophysical Society 2002 Annual Meeting, Symposium on Pumps and Transporters, San Francisco, CA. Lecture: *Molecular Dynamics Investigations of Transport in Aquaporins*

- April 3 2002, Indiana University, Bloomington, IN. Lecture: *The Physics of Photosynthesis*
- April 7 2002, 223rd American Chemical Society Meeting, Orlando, FL. Lecture: *Investigating the Mechanochemistry of Immunoglobulin, Febronectin and ATPase by Steered Molecular Dynamics*
- April 13 2002, UIC/UIUC Bioinformatics Symposium, Chicago, IL. Lecture: *Convergence of sequence and structure information in VMD*
- April 17 2001, NCSA NAMD workshop 2002, University of Illlinois, Urbana, IL. Lecture 1: *Introduction to Molecular Dynamics Simulations* Lecture 2: *What Can We Learn from MD Simulatlions?*
- May 4, 2002, Olga G. Nalbandov Symposium, Beckman Institute, University of Illinois, Urbana, IL. Lecture: *Membrane Channels in Action*
- May 7, 2002, Mayo Foundation, Biochemistry and Molecular Biology Department Seminar, Rochester, MN. Lecture: *Molecular Dynamics Investigation of Transport Aquaporins*
- May 9 2002, NCSA Alliance All-Hands Meeting, Urbana, IL. Keynote Address.
- May 14 2002, University of Maryland Scientific Computation Seminar, College Park, MD. Lecture: *Physics of the kidney: How it filters a bathtub of water a day without letting a proton pass*
- June 16-18 2002, Search Conference Development of Theoretical Methods for Complex systems, Schlo, Reisensburg, Germany. Lecture: *Structure-Sequence Graphics, Dynamic Modeling, Multi-Scale and Physical Analysis Tools for Nanometric Macromolecular Devices in Biological Cells*
- June 25-26 2002, INFMeeting 2002, Bari, Italy. Lecture: *Thermal Disorder in Bioelectronic Systems*

Other Resource members gave the following talks and poster presentations in the last year of the funding cycle:

- June 2001, Linux Clusters: HPC, University of Illinois at Urbana-Champaign (B. Isralewitz)
- June 2001, ESMTB Summer School, Siguenza, Spain (M. Dittrich, S. Park)
- July 2001, 4th International Conference on Biological Physics, Nagoya, Japan. (S. Hayashi)

- August 2001, Siggraph 2001, Los Angeles, CA. (J. Stone)
- August 2001, NAMD Workshop, Pittsburgh, PA.(J. Phillips, I. Kosztin, J. Gullingsrud)
- August 2001, HFSP Meeting, Heidelberg, Germany. (E. Tajkhorshid)
- October 2001, Cave Programming Workshop, Swedish Royal Institute of Technology. *Biomolecular Visualization with VMD and the Cave* (John Stone)
- October 2001, Visit with Collaborator, University of California at Pasedena. (M. Dittrich)
- November 2001, SC2001, Denver, CO. (J. Phillips)
- November 2001, LISA 2001, San Diego, CA. (T. Skirvin)
- April 2002, Biophysical Society Meeting, San Francisco, CA. (E. Tajkhorshid, R. Braun, B. Isralewitz, J. Gullingsrud, M. Sener, M. Gao, F. Zhu, S. Hayashi, S. Park, I. Balabin)
- May 2002, Scaling to New Heights Workshop, Pittsburgh Supercomputing Center, Pittsburgh, PA. *NAMD: Biomolecular Simulations on Thousands of Processors* (J. Phillips)
- May 2002, 2002 Alliance All-Hands Meeting, NCSA, Urbana, IL. (J. Phillips, K. Vandivort, R. Brunner, T. Skirvin)
- May 2002, Visit with Collaborator Julio Fernandez, Mayo Foundation, Rochester, MN (M. Gao)

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)

Key sites with links to the Resource web site include:

Biophysical Society

`http://www.biophysics.org`

Science Magazine

`http://www.sciencemag.org/`

`http://www.sciencemag.org/feature/plus/sfg/resources/res\_rschctr.shtml`

Nanomedicine by Robert Freidas at the Foresight Institute

`http://www.foresight.org/Nanomedicine/`

National Biomedical Computation Resource at San Diego Supercomputer Center

`http://nbcr.sdsc.edu/`

National Center for Research Resources at National Institutes of Health

`http://www.ncrr.nih.gov`

CMS Molecular Biology Resource at San Diego Supercomputer Center

`http://restools.sdsc.edu/`

`http://restools.sdsc.edu/biotools/biotools4.html`

Keck Computational Biology at Rice University

`http://www.bioc.rice.edu/`

`http://www-bioc.rice.edu/Keck/resources.html`

Collaborative Computational Projects for computer simulation of condensed phases at Daresbury Laboratory, UK.

`http://www.dl.ac.uk/CCP/CCP5/`

`http://www.dl.ac.uk/CCP/CCP5/links.html`

Biology Network of Modeling Efforts at the San Diego Supercomputer Center

http://bionome.sdsc.edu/

http://bionome.sdsc.edu/html/related.html

Bioinformatics and Computational Biology at George Mason University

http://science.gmu.edu/~michaels/Bioinformatics/

http://science.gmu.edu/~michaels/Bioinformatics/wwwsearchtools.html

BioMedNet

http://www.bmn.com/

http://links.bmn.com/lsearch/search/record?uid=BMLK.10118

BioInformer (A publication of European Bioinformatics Institute)

http://bioinformer.ebi.ac.uk/

http://bioinformer.ebi.ac.uk/newsletter/archives/2/vmd.html

Center for Structural Biology at Yale University

http://www.csb.yale.edu/

http://www.csb.yale.edu/userguides/graphics/vmd/vmd_descrip.html

Macromolecular Interactions Facility at University of North Carolina-Chapel Hill

http://macinfac.bio.unc.edu/

http://macinfac.bio.unc.edu/links.html

The Chemical Educator by Springer-Verlag

http://link.springer-ny.com/link/service/journals/00897/index.htm

http://journals.springer-ny.com/chedr/samplearticle2.html

BioNews NetScan

http://www.scitari.com/~bionews/

Science and Engineering Library at University of California at San Diego

http://scilib.ucsd.edu/

http://libnet.ucsd.edu/se/list.html?type=7

Frontiers in BioScience

`http://www.bioscience.org/current/currissu.htm`

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 our permission granting .

Finally, Dissemination efforts in earlier years of the past funding cycle yielded the following highlights:

- In 2000, we completed a major overhaul of the Resource's web site with a totally new design and more functionality. The research information on the site had been recently reorganized and thoroughly updated. Equipped with a new powerful search engine (`ht://Dig`) and several web-based databases, the site now offers easy access to Resource records such as publications, library checkin/checkouts, software users, mail addresses, hardware and software inventories, and acquisitions. Server Side Includes have become the Resource's core web management tool and AccessWatch web statistics provide a reliable measure of the effectiveness of the web site in generating and meeting community interests and needs (by section).
- In 2000 VMD and NAMD brochures were totally redesigned and a BioCoRE brochure was developed. The brochures have been used to announce the new VMD and NAMD versions and the first release of BioCoRE. They are posted on our web site and have also been mailed to over 500 research groups, institutions and individuals around the world. They are being distributed at events attended by the Resource members.
- Since 1999, all software manuals and documentation have been posted on our web site.
- In 1999 the Resource adopted new licenses for VMD and NAMD.

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