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Contents

This report describes research, development and service activities in 1999-2000 at the National Institutes of Health funded Resource for Macromolecular Modeling and Bioinformatics. The report covers the 10th funded year of the Resource. This is the third year of a five-year funding cycle awarded to the Resource.

The Resource continued to advance its computational tools for molecular biomedicine and demonstrated the value of its software and methods on a broad spectrum of research projects. The user base has grown, in particular, through the Resource web site `http://www.ks.uiuc.edu`. As in the past, the Resource directed its efforts to meet the following general goals:

- Advancing cellular biology through computational studies.
- Bridging a gap between laboratories where large biomolecular structures are discovered and measured, and computational laboratories where the expertise for very large scale molecular modeling resides.
- Engaging in relevant and demanding collaborations in cellular biology.
- Developing software to model and view ever-larger biomolecular units.
- Formulating theoretical concepts for the study of large biomolecular aggregates.
- Developing software for mechanical manipulation of biopolymers, for probing adhesive interactions and molecular recognition, and for interactive modeling.
- Broadening the scope of software development to include network-based collaborative tools.
- Exploring cost effective computer platforms and maintaining a state-of-the-art computational laboratory.
- Initiating service, training and dissemination activities.

All Resource activities saw last year great advances:

- Computational biology of cellular nanosystems has been further advanced through projects that demanded large scale modeling and that reached significant results.
- The visualization program VMD has become available on PCs running Windows, and through many algorithmic improvements it provides now with $250 graphics cards state-of-the-art molecular graphics that needed before special purpose workstations in a $10,000 price range.

- Development of the molecular modeling program NAMD has accurately anticipated that high end computing can be realized only on machines with thousands of processors; it is the only program for real-world research projects that runs efficiently on a few as well as a thousand processors on many types of machines.

- The Resource has pioneered the use of so-called steered molecular dynamics in which external forces are applied to test reaction pathways and mechanical properties of biopolymers as well as analyze the results. It is expected that half of all our future modeling calculations will soon be of this type. The Resource and its collaborators applied steered molecular dynamics in several new exciting research projects, for example,to understand the elasticity of muscle at the molecular level.

- The Resource has extended steered molecular dynamics to be used interactively by linking together VMD and NAMD, high performance computers, and a haptic device with six degrees of freedom, permitting manipulation of ongoing simulations while providing the user graphical and mechanical feedback.

- Finally, the Resource is developing a web portal for molecular biologists that will be a basis for communication and collaboration, and provide analysis tools to the community of computational and experimental researchers as well as serve to teach modeling and bioinformatics. This project is using the Resource software BioCoRE which saw a first release last year.

Research advances achieved through its unique modeling tools are a primary measure of the Resource's success, and motivate others to adopt these tools to advance computational biomedicine more broadly. The Resource collaborates on a number of ongoing projects: designing proteins that induce the growth of gold crystals by carrying out novel simulations of an oligopeptide at crystal surfaces; combining classical and quantum mechanical macromolecular descriptions develop an understanding of the functions of carotenoid-chlorophyll agregates in photosynthesis; explaining how membrane tension opens channels by molecular dynamics simulation of the stress-controlled gating of the ion channel MscL; determining the signaling mechanism of the *Ras* protein, implicated in numerous types of cancer, through a thermodynamic analysis of helix melting induced by GTP hydrolysis.

The Resource's unique combination of physical, chemical computational and biological researchers brings to each of these projects, a broad array of expertise.

Experimental groups at the Mayo Clinic and at the Bionegineering Department of the University of Washington in Seattle have continued their successful collaboration with the Resource on the mechanical properties of proteins in muscle (titin) and the extracellular matrix (fibronectin) using modeling in combination with observations to explain

previously unobserved prestretching phases in these proteins that contribute to functional elasticity and signaling. This ideal combination of single molecule experiments and theoretical modeling is regarded by leading researchers as one of the most fruitful areas of mechanistic molecular biology.

The purple membrane in *Halobacterium salinarium* of the archaea kingdom is a fascinating cellular structure, highly ordered yet fully functional as a light-driven proton pump fueling the cellular metabolism. On the basis of electron microscopy and crystallographic data, the Resource has used new features of its program NAMD to develop a complete atomic level model of the purple membrane, including proteins, all lipids, ions, and bulk water. For the first time a complete structure of a cellular machine, including its native environment is available. The Resource and its collaborators have been awarded a prestigious Human Frontier Science Program grant to exploit this structure and explore through observation and simulation light-induced proton pumping in ultimate detail.

Cellular structures often exceed the size that is amenable to molecular modeling calculation, even for the most advanced programs. Key examples include complexes of proteins and DNA, as in the case of multi-nucleosomal systems involved in genetic regulation and often in its disfunction. Using the theory of elasticity, the DNA component of such systems is readily modeled, but effective solution methods and testable predictions must be developed as well. Researchers at the Resource have joined an active and successful group of computational biologists in this field. Last year, through its own methodological contribution, the Resource made an important prediction of the loop geometry of DNA clamped by the *lac* repressor. The *lac* repressor was one of the first regulatory proteins studied and is an archetype system in regard to protein-DNA interactions. The predicted loop form was found to be in remarkable agreement with many observations and has revealed insights into straightforward mechanical strategies of DNA regulation. The work at the Resource will permit collaborators with the Resource to investigate other DNA-protein systems in the future, including the above mentioned multi-nucleosomal units.

A blue-light photoreceptor found in nerve layers of the eyes and brains has been another subject of a collaboration at the Resource. The receptor, cryptochrome, is known to play a prominent role regulating an animal's day-and-night rhythm. The research suggests that cryptochrome may be the site of a neurochemical reaction that lets birds, for example, process visual clues from the magnetic field and stay on course. Typical biomolecules interact with Earth's magnetic field too weakly to alter the course of their chemical reactions. Earlier experiments had shown, however, that certain chemical reactions involving so-called photo-induced radical pairs can be influenced by weak magnetic fields. The work at the Resource provided theoretical evidence that a biochemical reaction involving cryptochromes can be influenced by geomagnetic fields. If radical-pair reactions in

cryptochromes were connected by photoreception to the vision of animals, the magnetic field would modulate visual sensitivity. Behavioral biologists tested the proposed theory and found, among other surprising agreements, that many magnetic responses in animals require light.

The limited accuracy of molecular force fields remains an important obstacle in relating atomistic simulation to biomedical applications. The design of flexible force fields derived directly from the electronic Schrödinger equation is therefore a crucial goal in the development activities of the Resource. Our approach allows the simulation of chemically reactive molecules, and will enable accurate studies of enzyme function. Furthermore, and particularly in cases where molecules interact with light, quantum mechanical effects of the nuclei cannot always be neglected. Over the past year, we have made progress in extending first principles modeling methods that solve both the electronic and nuclear Schrödinger equations. Our first demonstrations have been on smaller molecules of biological relevance such as photoinduced cis-trans isomerization, spectroscopy of unsaturated hydrocarbons and photoinduced ring-opening reactions. These can be viewed as models for understanding the first events after photon absorption in the visual pigments and the synthesis of pre-vitamin D from 7-dehydrocholesterol. We have shown that direct computation of spectra is possible using our methods and will extend these methods to the spectroscopy of protein molecules. Recent advances have made time-resolved spectroscopy an important tool in resolving the mechanisms of enzyme function, and we will be able to simulate these events directly using the techniques that we developed over the last year. We have also begun to combine force fields with different levels of precision, using very accurate methods to treat the active site of an enzyme and less accurate methods to treat the surroundings. Our first such studies of cytochrome c oxidase, the terminal enzyme in the respiratory chain, have provided a detailed mechanism for the first half of the reaction which can and will be experimentally tested.

The Resource has intensified the development and distribution of NAMD, a parallel, object-oriented molecular dynamics code designed for high-performance simulation of large biomolecular systems. NAMD 2.1, with over 500 registered users, expands Tcl scripting and simplifies interactive simulation (IMD) while adding support for non-orthogonal periodic cells and the mollified impulse integrator, which reduces the frequency of full electrostatics evaluations. NAMD 2.2, approaching its first beta release, adds features needed to implement new simulation protocols, faster minimization, improved serial and parallel performance, and ports to Windows NT and the IBM SP.

During the past year, significant progress on parallel implementations of NAMD was made on several fronts. First, a port of NAMD to clusters of PCs running Windows NT was completed. This port will soon be released in the publically available version of NAMD. The port uses a new implementation of the Converse runtime system on

Windows NT. Good performance up to 16 processors has been observed, although further work in quantifying and improving performance on this platform is continuing. Second, new load balancing techniques were implemented in NAMD, including incorporation of a measurement based periodic rebalancer. The new strategies have given significant performance boost to NAMD, especially on a large number of processors. With a cut-off based simulation, we have shown speedups around 680 on 1024 processors of the ASCI Red machine, running on Intel Pentium based nodes. Further performance and scalability improvements as well as new parallel implementations of the Particle-Mesh Ewald (MPE) methods are ongoing.

Speeding up molecular modeling calculations through advanced parallel computing is only one route to improve the role of computing in molecular biomedicine; another route is improvement of algorithmic speed. The Resource has extended its molecular dynamics algorithm development to include fast "multigrid" methods for calculating electrostatic interactions among atoms. These methods are simpler than existing fast methods and combine better with advanced integration schemes. Preliminary tests indicate a high potential for improvement over existing methods. Also encouraging is work on the use of light Langevin damping for much longer time steps.

VMD is clearly the most widely used and, hence, most popular program of the Resource. It has found many converts due to its very advanced features, great speed and broad availability. During the last year VMD has been further improved. Beside making VMD available for the Windows operating system and thereby dramatically increasing the user base the developers at the Resource have extended the program's functionality and made significant performance improvements. Key features added include newly supported molecular dynamics trajectory file formats, rendering of transparent surfaces, support for 3-D trackers with haptic feedback capability, and direct connections to NAMD for interactive molecular dynamics simulations. Recent improvements in VMD algorithms resulted in a twenty to hundred-fold gains in performance when loading and working with large molecular systems containing 100,000 atoms or more.

In the past year the Resource has continued development of BioCoRE (Biological Collaborative Research Environment – supplement). BioCoRE is being developed to support four basic areas: Workbench, Notebook, Conferences, and Documents. The initial version of BioCoRE was released to the public on March 1 of this year, and already supports three of the four activity areas: Workbench, Notebook, and Conferences. In addition, researchers can use the BioCoRE interface to start VMD sessions on their local machines. The unique built-in evaluation component of BioCoRE has been implemented before the release to generate process and outcome data on all users and uses from the very beginning.

The Resource adopted early on a web-based services strategy and systematically developed its web site. The site has over 70,000 accesses a month and has become widely

popular as an information and teaching center in molecular biomedicine and as a distribution center for software. To support this rapidly growing service as well as the many demanding research projects, the Resource has consolidated the system servers.

The purchase and installation of a large number of visualization machines as well as the upgrade of the 3D projection facility have substantially enhanced our graphics capabilities. The projection facility has continued to evolve into an active research forum as well as into a popular teaching center.

The Resource's service, training and dissemination areas have enjoyed an exceptional year. Highlights include widely cited publications, new releases of the Resource's flagship programs NAMD (for molecular modeling), VMD (for molecular visualization, now available for Windows) and BioCoRE (Biological Collaborative Research Environment) and new licenses and structured registration process for all three programs; a redesigned web site; a meeting hosted at the Resource (titled: "Parallel MD Development and Use – Challenges and Opportunities") bringing together experts in parallel programming and experimental scientists for 2-day hands-on discussions; a new user database that allows systematic tracking of the Resource software users.

The services offered by the Resource have benefited a heterogeneous community of biomedical researchers, domestic and international. The number of visitors to the facility for training and service purposes has increased this year and their satisfaction has been documented. A large fraction of our user population is directly involved with medical research sponsored by the National Institutes of Health (NIH); an estimated 15% of the over four thousand users of VMD, NAMD, and BioCoRE are NIH supported.

The growing success and recognition of the Resource's research and development activities and the efforts to sustain high productivity and quality levels have resulted in new federal and other prestigious awards granted to the Resource. Additional spaces allocated to the facility at the Beckman Institute enable us to increase the number of researchers, developers and visitors.

The Purple Membrane in Halobacteria Fuels the Cells' Metablism Through Proton Pumping

Cells fuel their metabolism by means of a hierarchy of energy conserving steps, the primary step being generation of a potential across cellular membranes through vectorial transport of protons. In most cells, the machinery involves several types of membrane proteins, but in *Halobacterium salinarium* it involves only a single type of protein, bacteriorhodopsin (bR). This protein is arranged in an ordered, hexagonal array called the purple membrane* [1, 2].

Its remarkable simplicity makes the purple membrane an ideal target for studies in bioenergetics. This is compounded by the close relationship between bR and the rhodopsins that act as light detectors in animal vision, as well as a relationship of bR to G-protein coupled receptors, which are important drug targets. Until recently, progress in the study of the purple membrane had been hampered by lack of structural information at the high resolution level necessary to understand the system's function. However, knowledge has improved dramatically through a combination of electron microscopy [3] and crystallographic [4–6] investigations that yielded the structure of bacteriorhodopsin and some of its associated lipids. Computer modeling has now succeeded in combining all available structural data and building an atomic level model of the purple membrane [7]. For the first time, a structure of an entire cellular apparatus, including all protein components, lipids, ions and water, is available. On this basis the physical mechanism of a key bioenergetic function can be explained in ultimate detail.

The construction of the purple membrane reported in [7] relied upon the Resource's molecular dynamics program NAMD into which had been integrated a set of advanced modeling features. NAMD now permits simulation of a periodic hexagonal array under constant pressure and temperature conditions and can account in full for electrostatic interactions important at membrane-water interfaces. The hexagonal unit cell of our purple membrane model contained 23,700 atoms distributed over protein, lipid, ion, and water components. The initial model was equilibrated at 1 atm until the structure settled after 1 ns. The physical characteristics of the purple membrane were characterized in subsequent simulations. The structure will serve researchers to study the proton pump cycle of the purple membrane both through observation and further modeling.

Researchers at the Resource have developed, in anticipation of the described development, a description of the potential surfaces of the ground and electronically excited states that govern the photodynamics of the purple membrane's retinal chromophore (see subproject on page 17) [8]. They have also improved the simulation of water molecules

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

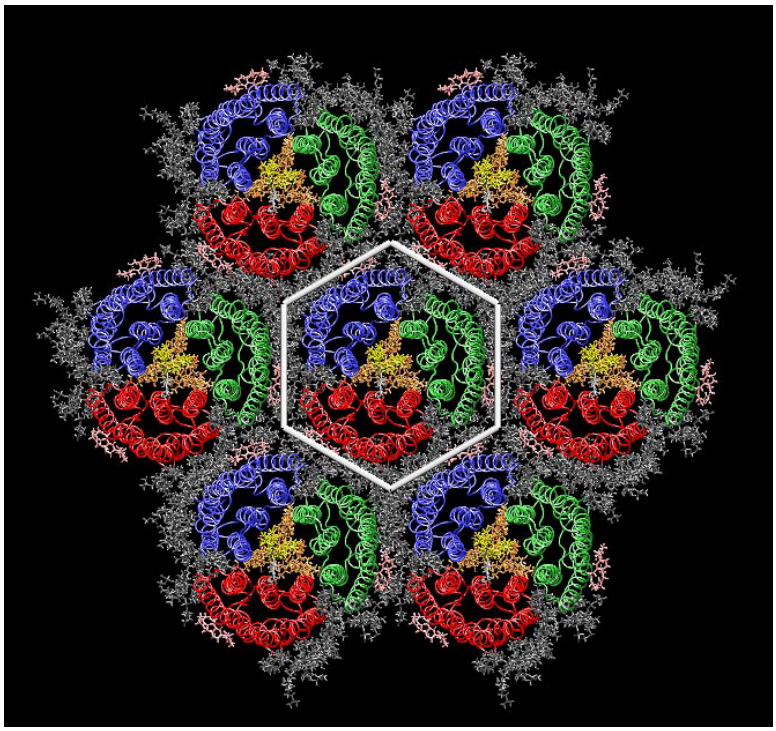

Figure 1: Top view of a purple membrane patch that includes 21 bacteriorhodopsins in seven adjacent unit cells. The hexagonal unit cell is shown in the middle of the patch, its boundary indicated by white lines.

residing in bacteriorhodopsin [9] and have extended NAMD to describe quantum mechanical dynamics of proteins [10], needed to account properly for the 600 femtosecond phototransformation of retinal that triggers proton pumping.

Steered Molecular Dynamics Studies of Ions in a Potassium Channel

Ion channels are membrane-spanning proteins that form pathways for the flux of inorganic ions across cell membranes [11]. Among their many functions, ion channels regulate the secretion of hormones into the bloodstream, generate the electrical impulses underlying information transfer in the nervous system, and control the pace of the heart and of the muscle system [11]. Recently, the crystal structure of the K^+ channel from *Streptomyces lividans* (KcsA channel) was resolved [12]. The channel is approximately 45 Å long and consists of an inner pore (starting from inside the cell), a large cavity near the middle of the pore, and the so-called selectivity filter that separates the cavity from the extracellular medium. The inner pore and the internal cavity are hydrophobic regions; in contrast, the selectivity filter is lined exclusively by polar carbonyl groups belonging to the so-called "signature sequence". Mutational studies [13, 14] showed that this "signature sequence", composed of eight amino acids, is responsible for the channel's 10,000-fold selectivity of potassium over sodium.

The channel achieves its high-fidelity discrimination between potassium and sodium ions while maintaining nearly diffusion-limited throughput. Intriguingly, the channel appears to rely upon the interactions of multiple ions in the channel to accomplish this. In their report of the crystal structure of the KcsA channel [12], the authors proposed that ions are attracted to binding sites within the selectivity filter, while mutual repulsion between ions in the cavity and in the filter disrupts the binding of the ions in the filter and speeds conduction.

The Steered Molecular Dynamics (SMD) approach [15–17] was used to simulate the permeation of ions through the selectivity filter in order to further elucidate the interactions between ions and the protein which give rise to such an efficient selectivity process.* Three simulations of 1–2 ns duration were conducted using the program NAMD [18]: the first began with a single K^+ ion placed in the central cavity, while the other two began with one ion in this cavity and another in the filter region binding site closest to the cavity. In each simulation, a harmonic restraint was applied to the ion in the central cavity and moved with constant velocity through the filter, resulting in the permeation of both ions through the channel. The SMD module of NAMD was modified to permit a simulation protocol in which ion motion was unbiased within the plane of the membrane, while the progress of the ions along the length of the filter was guided by a harmonic restraint moving at constant velocity. The system, including the lipid bilayer and surrounding water in which the protein was embedded, contained over 38,000 atoms.

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

Two important results were obtained from these simulations. First, in all three simulations, the ion or ions moved in a stepwise fashion from binding site to binding site. At each site, the K^+ ions were coordinated by 2–4 carbonyl oxygens of the selectivity filter backbone. The stepwise movement of the ions is evident from a plot of the applied force, as shown in Fig.2.

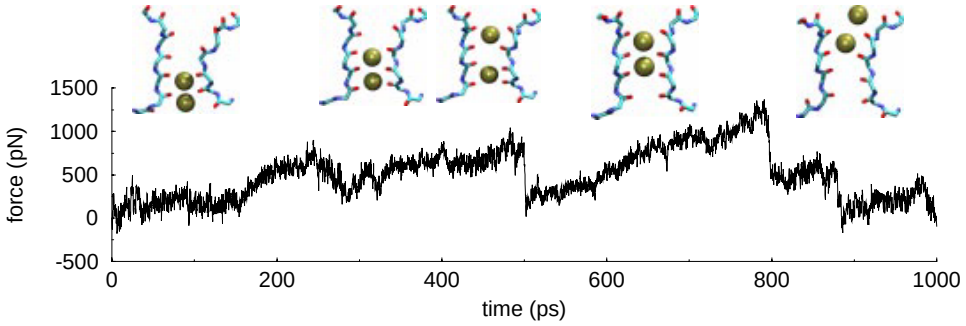

Figure 2: Applied force during a 1 ns SMD simulation of two K^+ ions in the KcsA channel. The peaks in the applied force correspond to discrete hops between ion binding sites. The hops are illustrated by snapshots from the simulation at the corresponding points in time.

The second result concerns the dynamics of the filter during the simulated permeation. During the setup and minimization of the protein structure, several residues in the selectivity filter region assumed a conformation in which the carbonyls were pointing away from the pore. It was observed in each of the SMD simulations that when ions approached the refolded parts of the filter, the carbonyl oxygens swung around to form favorable interactions with the ions. Flexibility of the selectivity filter backbone has been noted elsewhere [19], but in this study we see that even in a nonequilibrium state, the ions contribute significantly to the stable structure of the protein.

NAMD: Scalable Molecular Dynamics

NAMD is a parallel, object-oriented molecular dynamics code designed for high performance simulation of large biomolecular systems [18].* NAMD is distributed free of charge as both source code and convenient precompiled binaries for massively parallel supercomputers, workstation clusters, and, soon, PCs running Windows NT. The most recently released version of NAMD has over 500 registered users. NAMD 1.0 [20] was developed in 1995 to run on the Resource's 8-processor HP workstation cluster. By 1998, NAMD 2.0 was able to employ 128 processors of a Cray T3E. NAMD 2.2, due to be released this summer, has demonstrated useful speedups on over 1000 processors of the ASCI Red (Fig. 3). Driven by new techniques such as interactive modeling which demand even higher simulation rates, the Resource will continue to improve the performance and efficiency of NAMD in the coming year.

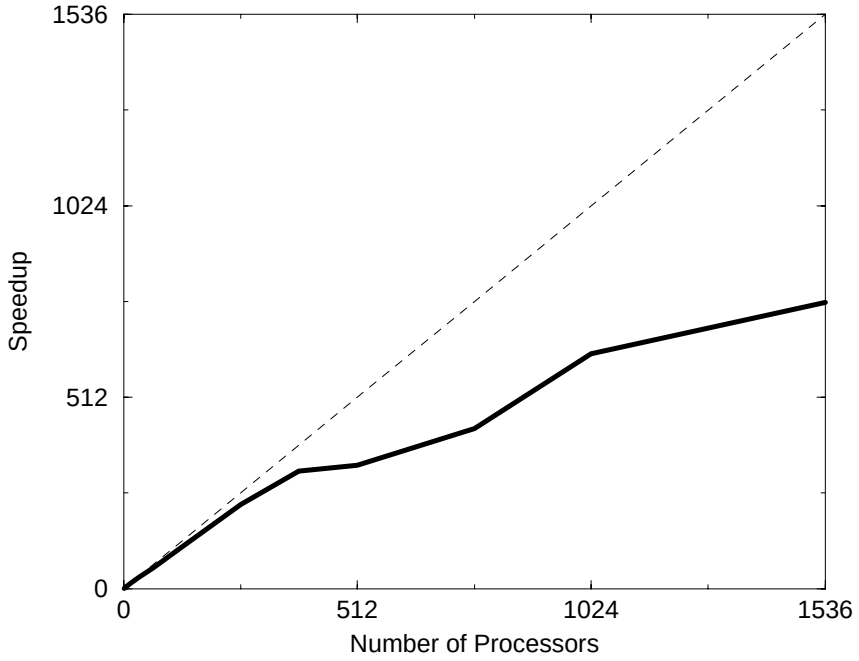

Figure 3: Scaling of NAMD on the ACSI Red for a 92,000 atom simulation.

The simulation rate achieved by NAMD has been improved by optimizations to the serial algorithm, by new measurement-based load balancing techniques, and by the new mollified impulse method integrator. Development in these directions has been complementary; a 10% serial performance improvement was achieved while working to eliminate

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

bottlenecks observed only on 512 processors. Similarly, the mollified impulse method has reduced the impact of the less well parallelized long-range electrostatics evaluation.

Current development effort is centered on improving the performance of long-range electrostatics calculations. The popular particle mesh Ewald (PME) algorithm contains a serial calculation (the reciprocal sum) which limits NAMD's scalability on machines with over 64 processors. The NAMD achitecture will allow this calculation to be distributed to a small subset of processors and interleaved with other more-easily parallelized portions of the simulation.

The Resource is also applying its expertise in numerical analysis to the long-range electrostatics problem. A newly developed method combines the $O(N)$ complexity and reduced communication of multigrid methods with the analytical derivatives of PME. The method may be applied to systems which are periodic in 0, 1, 2 or 3 dimensions. Depending on the performance achieved, this algorithm may replace all other long-range electrostatics methods currently employed by NAMD. Also under study is the use of light Langevin damping to greatly reduce the frequency of full electrostatics evaluations.

The total time required to complete a simulation with NAMD is also influenced by the researcher's ease in setting up the simulation and employing new and efficient protocols. NAMD has addressed these issues by the addition and extension of backwards-compatible scripting implemented with the standard language Tcl. End users can set and access variables, include other files, checkpoint and revert the simulation, call measurement functions, and compose new simulation protocols.

The benefits of this development have exceeded their goals—the implementation of checkpoint and revert features for a new simulation protocol (CONTRA) also allowed the implementation of efficient energy minimization (conjugate gradients). This effort is being extended to include a separation of the NAMD computational engine and its user interface into distinct modules. As a result, NAMD will be usable as a library by VMD and other programs while experimental serial codes will assume a familiar interface.

VMD: High Performance Molecular Graphics

VMD [21] is a molecular visualization program for static and dynamic molecular structures. VMD* is designed to facilitate and advance biomedical research and is used by computer experts and non-experts alike. VMD provides interactive 3-D molecular visualization and analysis capabilities, an extensive scripting language, and the ability to read many molecular file formats. VMD 1.4 was released on January 7, 2000. More than 3000 users have registered and downloaded VMD 1.4 since its release. Of the 3000 registered users, 400 are NIH funded researchers.

During the past funding period, development efforts were focused on completing the Windows version of VMD (VMD 1.4), thus making the program available to a much wider user community. With the release of the Windows version, the number of VMD users has approximately doubled. VMD 1.4 has made it possible for users of a PC costing less than two thousand dollars to perform the same molecular visualization tasks that just three years ago would have required a high-end workstation costing tens of thousands of dollars. VMD takes maximum advantage of present and future 3-D graphics accelerators on both PCs and workstations through the use of the OpenGL graphics library.

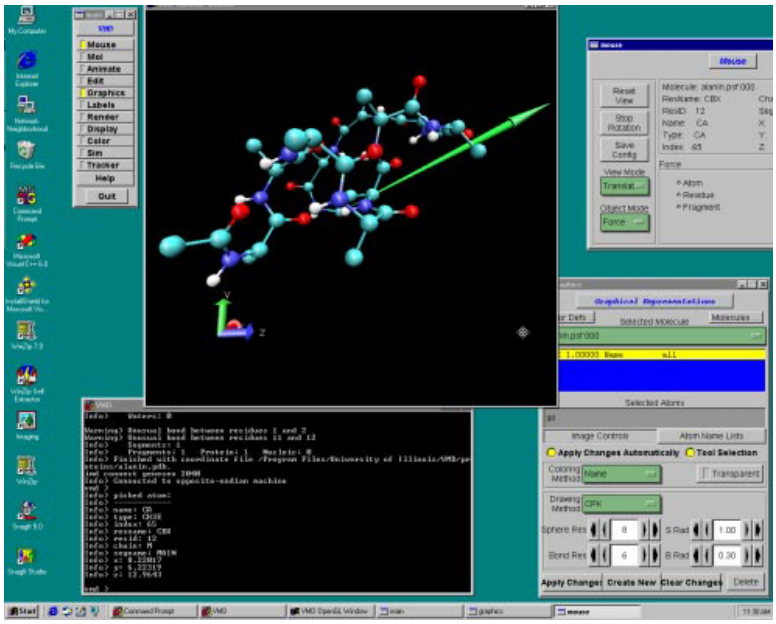

Figure 4: VMD performing an interactive MD simulation on Windows NT

VMD 1.4 contains many efficiency improvements due to the use of more sophisticated internal data structures and algorithms. These improvements make VMD much more effective when working on systems containing more than 100,000 atoms: structure files are loaded twenty time faster, and distance-based atom selections are performed fifty to

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

one hundred times faster. The improvements to portability, rendering algorithms, and overall efficiency have been essential steps in making VMD usable on personal computers. Other new features in version 1.4 include a 'screen door' transparent surface rendering algorithm, improved depth cueing for 3-D perception when viewing complex molecules, a software interface which allows VMD to interoperate with a large variety of 3-D input devices including haptic feedback devices, built-in support for several additional molecular dynamics trajectory file formats, and interactive molecular dynamics simulation features.

VMD 1.5, currently under development, will add new features and enhance user friendliness. The 3-D rendering engine in VMD will be updated with new graphics algorithms which will improve the visual quality of many molecular representations while maintaining or exceeding current interactive rendering performance. Enhancements will be made to VMD to improve support for data and databases located on the internet and the web. New collaborative features will be added to VMD to support the BioCoRE collaboratory project.

BTA UNIT: T

TITLE: Characterization of Conical Intersections between the Ground and First Excited State for a Retinal Analog

KEYWORDS: Bacteriorhodopsin, retinal protonated Schiff base, polyenes, photoisomerization, quantum chemistry, conical intersection

AXIS I: 8, 9, 25b

AXIS II: 74c

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% BRTP $: 4%

ABSTRACT: The all-trans retinal protonated Schiff base (RPSB) is the chromophore of bacteriorhodopsin (bR), a transmembrane protein that acts as a light-driven proton pump in halobacterium salinarium, converting light energy into a proton gradient [22–24]. As its name indicates, bR is closely related to rhodopsin, the protein which acts as the primary light detector in the visual pathway of higher life forms.

Upon absorption of light, the chromophore undergoes a photoisomerization process (all-*trans* → 13-*cis* in bR) that eventually provides the driving force for the translocation of protons. This elementary photoisomerization process proceeds on two coupled potential energy surfaces: following the absorption of a photon, ground state population is transferred to the first excited state and the ensuing intramolecular dynamics finally leads to transfer of excited state population back to the ground electronic state. This population transfer is expected to be most efficient in regions of the potential energy surface where the ground and excited states are nearly or exactly isoenergetic, for example at a conical intersection.

We extended and improved our previous quantum mechanical studies of the photoreaction dynamics in the protein [10], studying the first excited electronic state of a retinal protonated Schiff base analog (all-trans-3,7-dimethylnona-2,4,6,8-tetraene-methyliminium cation) with accurate quantum chemistry methods. This model of

the retinal chromophore in bR includes ten conjugated π electrons as well as two pertinent methyl groups on retinal's backbone, and an additional methyl group that replaces the Lys216 link of the chromophore.

We started the calculations with an investigation of the excited state local minimum and conical intersection that are relevant for isomerization in bR, rotation around the C_{13}=C_{14} bond [8]. The calculations show that the excited state local minimum is close (both energetically and geometrically) to a conical intersection that furnishes a gateway back to the ground state potential energy surface. We have identified the two global coordinates that are expected to be most effective in promoting efficient internal conversion back to the ground state. Surprisingly, these coordinates are the C_{13}=N_{15} stretch and C_{13}=C_{14} torsion, instead of the expected C_{13}=C_{14} stretch and torsion.

We are currently studying other local minima and conical intersections in the all-trans RPSB analog in order to determine how the bR protein selects the bond which will isomerize and why the outcome is different in the protein and solution phase environments [25].

BTA UNIT: T

TITLE: Molecular Dynamics Simulation of the Mechanosensitive Ion Channel MscL

KEYWORDS: mechanosensitive ion channel, molecular dynamics, MscL

AXIS I: 2, 7a

AXIS II: 74f, 74h, 77

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ABSTRACT: Mechanosensitive (MS) channels play an important physiological role in living cells of diverse phylogenetic origin. They are ubiquitous in prokaryotes, and have recently been characterized in archaebacteria [26] as well as mammals [27,28]. In bacteria, a controlled response to the osmolality of the environment is essential for the survival of the cell. In *E. coli*, three MS channels have been identified, and one of these, MscL, has been cloned [29]. Several studies [30–32] have confirmed the importance of this channel for osmoregulation of the bacterial cell.

The dynamics of MscL within a lipid bilayer environment would help to evaluate models of the gating of MscL in response to membrane tension, or even to suggest new mechanisms for the gating process. Molecular dynamics simulations gave a detailed picture of the dynamics of the protein and membrane on the time scale of a few nanoseconds. While this time is too short to observe channel gating, there are several aspects of channel function that could be addressed by a molecular dynamics analysis. First, examination of specific protein-lipid interactions will shed light on how the protein gate can be controlled by membrane tension alone. Second, the dynamics and environment around specific residues will explain the results of mutagenesis experiments. Finally, the overall rigidity or flexibility of the protein may give us some insight into the gating mechanism of MscL.

Preliminary results have been obtained from a 2 ns simulation of MscL embedded in a POPC lipid bilayer with surrounding water; the simulated system contains over

52,000 atoms.* Analysis of the fluctuations of the C_α atoms in the ten transmembrane helices revealed that the protein is most rigid in the gating region formed by the N-terminal part of the first transmembrane helices of each subunit. This result is in agreement with recent electron spin resonance measurements. We plan to analyze correlated movements in the protein, study the role of key residues implicated in mutagenesis experiments, and examine the interactions between the protein and the surrounding bilayer.

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

BTA UNIT: T

TITLE: Dynamics of the Selectivity Filter in the Potassium Channel KcsA

KEYWORDS: KcsA, potassium channel, steered molecular dynamics

AXIS I: 2, 9

AXIS II: 74b,c,h

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DEGREE2: Ph.D.
DEPT2: Beckman Institute
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% BRTP $: 2%

ABSTRACT: Steered Molecular Dynamics (SMD) simulations were carried out to elucidate the ion-ion and ion-protein interactions involved in K^+ ion permeation in the potassium channel KcsA*. Initial coordinates for the protein were taken from the crystal structure (PDB entry 1bl8). The protein was embedded in an equilibrated solvated palmitoyl-oleoyl- phosphatidylcholine (POPC) lipid bilayer consisting of 100 lipids in each leaflet, constructed earlier in our group [33]. The lipid headgroups were converted to phosphatidyl-ethanolamine (PE) and phosphatidyl-glycerol (PG) in the experimentally observed ratio of 3:1 [34]. After inserting the protein and removing overlapping lipids and water molecules, the complete structure contained 38,112 atoms, including 134 lipids and 5117 water molecules.

The system was equilibrated at 305 K with an isotropic pressure of 1 atm [35] for 1 ns. Three SMD simulations were conducted under conditions of constant volume, beginning from this equilibrated structure. In addition, 2 ns of constant-pressure unsteered dynamics were performed with one ion in the central cavity and one ion in the first binding site. During the free dynamics, the dihedral angles in the selectivity filter region of the protein were essentially unchanged. During all three SMD simulations, however, sharp transitions in several dihedrals were observed which resulted in improved coordination of the permeant K^+ ion and stabilization

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

of the protein-ion complex. These SMD simulations suggest that permeant K^+ ions play a structural role in stabilizing the orientation of the carbonyl groups in the selectivity filter.

BTA UNIT: T

TITLE: Ras protein: a vital biomolecular switch

KEYWORDS: G-proteins, GTPase, GTP hydrolysis, molecular switches, molecular dynamics

AXIS I: 9

AXIS II: 74h, 84

INVEST1: Ioan Kosztin
DEGREE1: Ph.D.
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INVEST2: Robijn Bruinsma
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% BRTP $: 5%

ABSTRACT: Ras, a protein of 166 amino acids, is a member of a super-family of regulatory G-proteins with a common structural core [36]. Ras hydrolyzes guanosine triphosphate (GTP) to perform a signaling task. The G proteins play a key role in conveying extra-cellular information from the cell exterior to the rest of the cell. The signals transduced by GTPases such as Ras are transient, linking activated hormonal "receptors" to "effector" molecules (both embedded in the cell surface). G proteins are biomolecular switches and timers: in their resting state, they bind to the "low-energy" GDP molecule; after activation of the receptor by a hormone, the G protein exchange GDP for the "high-energy" GTP molecule, setting the G-switch "on"; then, the G protein binds to, and activates the effector; after a time of the order of seconds, the G protein hydrolyzes GTP and dissociates; the G-switch is turned "off". The cycle continues as long as the hormonal effector stays activated. Understanding the functional mechanism of these G-switches is important since precursor to oncogenic mutants of Ras are found in 25 to 30% of human tumors.

Based on the recently determined crystallographic structure of the Ras+GAP (effector) complex [37], we employ molecular dynamics (MD) simulations to examine the mechanism of Ras signaling. MD simulations will be employed also to investigate the effects of mutants, in particular, at the oncogenic site.

BTA UNIT: T

TITLE: Ab Initio Studies of Intermediates in Cytochrome c Oxidase

KEYWORDS: cytochrome, oxidase, ab initio, reaction cycle

AXIS I: 2, 9

AXIS II: 74a

INVEST1: D. B. Moore
DEGREE1: B.S.
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% BRTP $: 3%

ABSTRACT: Cytochrome c oxidase is a transmembrane protein and is the terminal enzyme in the respiratory chain. The oxidase converts four electrons, eight protons, and an oxygen molecule into water and electrochemical energy stored in the form of a pH gradient across the mitochondrial cell membrane.

Recently, several crystal structures have appeared [38–40] serving as a starting point for theoretical studies of the mechanism. We have set out to complete the crystallographic information by determining the ligands and residue protonation states in the binuclear Cu-Fe center that serves as the enzyme active site. We carried out ab initio quantum chemical studies of a model of the active site (containing more than 300 explicit electrons) at the Hartree-Fock, density functional theory (DFT) and localized Möller-Plesset levels of theory [41]. We optimized the geometries of the possible ligands, including all reasonable combinations of differing numbers of water and hydroxide ligands.

The resulting local minima were characterized energetically and used to develop a mechanism for the first half of the CcO reaction cycle, prior to the binding of molecular oxygen. Our calculations predict two nearly isoenergetic forms of the oxidized enzyme, differing in the ligands present. This is in accord with experimental studies which show "fast" and "slow" forms of the oxidized enzyme, differing in both their spectroscopy and their reactivity toward CN^-.

Our calculations are able to further identify these species at the molecular level. The mechanism which results from our calculations is in strict accord with the electroneutrality principle (every electron transfer is accompanied by a proton transfer), even though this was not assumed. Future work will focus on the explicit treatment of the surrounding protein, dynamics of coupled electron and proton transfer, and the oxidative phase of the reaction cycle.

BTA UNIT: T

TITLE: Membrane protein dynamics in the photosynthetic unit of purple bacteria

KEYWORDS: Light-harvesting complexes, excitation transfer, electron transfer, molecular dynamics

AXIS I: 2, 7a

AXIS II: 74c,f,h

INVEST1: Ana Damjanovic
DEGREE1: B.S.
DEPT1: Department of Physics
NONHOST1:

INVEST2: Thorsten Ritz
DEGREE2: B.S.
DEPT2: Department of Physics
NONHOST2:

INVEST3: Justin Gullingsrud
DEGREE3: B.S.
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% BRTP $: 1%

ABSTRACT: Photosynthetic organisms fuel their metabolism with light energy and have developed for this purpose an efficient apparatus for harvesting sunlight. The latter apparatus, referred to as the photosynthetic unit (PSU), is an aggregate of several pigment-protein complexes. For purple bacteria, the atomic level structure of the entire PSU is known [42–46]. The function of the PSU is to absorb light and to funnel the light energy, in a series of excitation transfer steps, from the satellite light-harvesting II (LH-II) complexes to the core light-harvesting complex I (LH-I), and, finally, to the photosynthetic reaction center (RC)*.

We have studied the quantum mechanics of excitation transfer in the absence of thermal and structural disorder [47–49]. To study the influence of protein dynamics at physiological temperatures on the electronic excitations in LH-II, we have established a computational model of LH-II in its natural lipid-water environment

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

(75,000 atoms). Through molecular dynamics simulations of this system, we will investigate the fluctuations of the protein. We plan to study the influence of these fluctuations on the delocalization length of LH-II exciton states and the excitation transfer rates within LH-II. The combined molecular dynamics/quantum mechanics study of LH-II that we will accomplish, is a prototype for studying the role of disorder on elementary biological processes involving electronic degrees of freedom, e.g., enzyme reactions.

The coupling between protein dynamics and electron transfer has been studied in the framework of the spin-boson model and has been applied to molecular dynamics simulations of the RC from *Rps. viridis* in vacuum [50]. With a model of the structure of LH-I from *Rb. sphaeroides* now available [46], we will describe the dynamics of the RC from *Rb. sphaeroides* in its natural environment of the LH-I complex. Understanding of the RC dynamics will provide insight into the physical mechanism underlying redox processes in mitochondria.

BTA UNIT: T

TITLE: Magnetic sensors in vertebrates

KEYWORDS: Magnetoreception, radical-pair processes, cryptochromes, photoreceptors

AXIS I: 1d, 25

AXIS II: 74h

INVEST1: Thorsten Ritz
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DEPT1: Department of Physics
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INVEST2: John B. Phillips
DEGREE2: Ph.D.
DEPT2: Department of Biology
NONHOST2: Indiana University

% BRTP $: 1%

ABSTRACT: Magnetoreception in vertebrates is one of the few sensory mechanisms for which no receptors have been identified and the biophysical mechanism remains unknown. It has been suggested earlier that magnetoreception can be achieved through a chemical sensor based on molecules engaging in radical-pair processes [51]. In a theoretical study, we established a model for a magnetoreception organ, consisting of an orientationally ordered system of molecular substrates undergoing radical-pair processes*. Computational modeling showed that a magnetic field as weak as the earth's magnetic field (0.5 Gauss) can produce significant biochemical effects on this model magnetoreception system. The behavioral responses predicted by this model can explain experimental observations, such as the need for blue-green ambient light for magnetic compass orientation of birds and newts [52, 53].

The studies in [54], carried out at the Resource, suggest an involvement of the blue-green photoreceptor chryptochrome in magnetoreception. Fruitflies *Drosophila melanogaster* have been shown earlier to exhibit magnetic compass orientation [55]. We plan to use the same behavioral assay as in [55], but for mutant strains of fruitflies lacking cryptochromes, to investigate whether the latter are involved in magnetoreception.

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

BTA UNIT: T

TITLE: Analysis Tools for Teraflop Molecular Dynamics Simulations

KEYWORDS: Molecular dynamics, non-equilibrium statistical mechanics, stochastic methods, time series analysis

AXIS I: 9

AXIS II: 74h, 84

INVEST1: Ioan Kosztin
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DEPT1: Beckman Institute and Department of Physics
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% BRTP $: 6%

ABSTRACT: The Resource is developing a library of Molecular Modeling Tools* (MMTools) for the analysis and processing of molecular dynamics (MD) simulation data. The need for MMTools is motivated by the increased scope of MD simulations in biomedicine today. MMTools is devised as an extendible set of modular routines, which can be invoked by the user through Tcl scripts for processing MD data of completed simulations. Furthermore, the Tcl implementation of the MMTool routines will make them accessible directly from: (1) our molecular dynamics program NAMD†, for on-the-fly monitoring and analysis of an ongoing MD simulation, and (2) our molecular visualization program VMD‡, for sophisticated quantitative analysis during the visualization of biomolecules.

Initially, MMTools will comprise the following ten tools: (1) correlation functions – for calculating equal-time-, auto- and cross-correlation functions [56]; (2) principal component analysis – for identifying and characterizing slow modes in proteins [57]; (3) linear response theory – for investigating the response of a biomolecular system to an external weak perturbation [58]; (4) hysteresis – for analyzing the nonlinear and time-delayed response of a system to a periodical external perturbation [58]; (5) echoes – for studying the coherent excitations of protein modes via consecutive sudden perturbations [59]; (6) time series analysis – for reaction coordinate analysis and for reconstruction of potential of mean force (PMF) [60]; (7) mean

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

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

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

first passage time analysis – for describing potential barrier crossing events [61]; (8) spin-boson model – for modeling spectral line shapes and (potential) curve crossing phenomena in proteins [62]; (9) vector quantization of protein dynamics – for determining topologically discrete representations of manifolds covered by protein dynamics [63]; and (10) a test suite – for testing the functionality and performance of the currently available MMTools for three sample systems of different size, i.e., a small protein (1000 atoms), a medium protein-water system (10,000 atoms), and a large protein-lipid-water complex (100,000 atoms).

BTA UNIT: T

TITLE: Electronic Absorption and Resonance Raman Spectroscopy from Ab Initio Quantum Molecular Dynamics

KEYWORDS: Electronic absorption spectra, resonance Raman spectra, excited states, polyenes, ab initio, quantum molecular dynamics

AXIS I: 7a, 8, 9, 25b

AXIS II: 74c

INVEST1: Michal Ben-Nun
DEGREE1: Ph.D.
DEPT1: The Beckman Institute and Department of Chemistry
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% BRTP $: 4%

ABSTRACT: The conversion of light to mechanical energy is often required in the context of biology and molecular switching. The most straightforward means of accomplishing this is through photoinduced cis-trans isomerization in unsaturated systems, as it occurs in the rhodopsin family of proteins. Experimentally, these isomerization reactions are most often studied using spectroscopic methods, e.g., electronic absorption and resonance Raman spectroscopy, whose detailed interpretation may be treacherous. To simplify the task of interpreting these spectra, we are developing the use of *ab initio* quantum molecular dynamics [64–68] as a method for simulating absorption and resonance Raman spectra directly. We have chosen the absorption spectrum of ethylene as a first test case because it is a small molecule amenable to accurate theoretical treatment and extensive experimental information is available for comparison.

Using our *ab initio* molecular dynamics method and the correlation function formalism for molecular spectroscopy we have calculated the absorption and resonance Raman profiles of ethylene following $\pi \rightarrow \pi^*$ excitation [69]. We were unable to obtain quantitative agreement with experiment [70], but many of the qualitative features were correctly predicted (e.g., excited state lifetime, fundamental activity in all totally symmetric modes with the C=C stretching mode being the most dominant, overtone activity in the torsional motion, out-of-plane wagging motions and the out-of-plane rocking motions).

In the future, we will try to obtain quantitative agreement with experiment by improving the accuracy of the quantum chemistry methods that we use, and we

will also apply this approach directly to spectroscopy in protein molecules using empirical force fields to describe the ground and excited electronic states.

BTA UNIT: T

TITLE: Ab initio Studies of Ring-Opening in Photoexcited Cyclobutene

KEYWORDS: Excited states, ring-opening, stereochemistry, Woodward-Hoffmann rules, *ab initio* molecular dynamics

AXIS I: 2, 9, 18

AXIS II: 74c

INVEST1: Michal Ben-Nun
DEGREE1: Ph.D.
DEPT1: The Beckman Institute and Department of Chemistry
NONHOST1:

% BRTP $: 2%

ABSTRACT: Photochemically-induced ring-opening reactions are important in the biological synthesis of vitamin D. A critical aspect of these reactions in that context is the stereoselectivity, which is predicted by the Woodward-Hoffmann (WH) rules [71]. The simplest molecule in which this stereoselectivity can be studied is the electrocyclic ring-opening reaction of cyclobutene to 1,3 butadiene. This molecule is also interesting as a paradigm for cases where the WH-predicted stereoselectivity is not observed, since experiments on alkyl-substituted cyclobutenes have shown the photoproducts to be both WH-allowed (disrotatory) and forbidden (conrotatory) [72]. Because of controversies in the assignment of some bands [73], the interpretation of resonance Raman experiments [74], which provide a more direct probe of the excited state dynamics, has also been questioned.

Using excited state *ab initio* "on-the-fly" molecular dynamics simulations* we have directly probed the photodynamics of cyclobutene [75]. This first-principle investigation provides, for the first time, direct evidence for immediate disrotatory ring-opening motion on the excited electronic state. Our simulations show that the preference for the WH-predicted stereochemistry is established within ∼15 fs after the electronic excitation and is therefore in principle observable via resonance Raman spectroscopy. To resolve the controversy regarding the interpretation of the resonance Raman spectra we have carefully analyzed the character of the local- and normal-mode coordinates. Our analysis suggests that the experimental spectrum does not provide direct evidence for a disrotatory motion (because the overtone of

*URL: `http://hobbes.scs.uiuc.edu/Research/AIMS/Cyclobutene/Cyclobutene.htm`

interest is masked by intense scattering from butadiene photoproduct). Therefore, future experiments are needed to confirm the theoretical predictions.

Future studies will extend this work to longer time scales in order to investigate the mechanism by which photoexcited cyclobutene decays back to the ground electronic state and to the larger cyclohexadiene molecule which is directly relevant to vitamin D synthesis.

BTA UNIT: T

TITLE: Interactive Molecular Dynamics

KEYWORDS: molecular visualization, molecular graphics, interactive simulation

AXIS I: 9

AXIS II: 42, 89

INVEST1: John Stone
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DEPT1: Beckman Institute
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INVEST2: Justin Gullingsrud
DEGREE2: B.A.
DEPT2: Department of Physics
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% BRTP $: 5%

ABSTRACT: The Resource has recently developed extensions to its simulation and visualization programs NAMD [18] and VMD [21] which provide the ability to interact with running molecular dynamics simulations through the use of a novel input device. In this system, termed interactive molecular dynamics (IMD), a researcher uses a haptic device to apply forces to atoms in a simulation. The haptic device transmits forces back to the hand of the researcher, which conveys information about the response of the system while guiding the researcher in steering the selected atoms. The IMD connection between VMD and NAMD uses a light-weight TCP/IP socket library which can be readily adapted to other visualization and simulation programs. In addition, VMD can record applied force and atom coordinates to allow further analysis using VMD's built-in analysis and user extensible scripting features.

This work improves upon previous technology developed by the Resource, collectively known as MDComm [76], which provided a more limited mode of interaction between the user and the simulation. The IMD system is much more portable, already supporting many versions of Unix as well as Windows. Unlike MDComm, which required a fairly complicated installation and setup procedure, the IMD functionality in NAMD and VMD is entirely self-contained. Finally, the light-weight nature of the IMD components as well as a design based on direct host-to-host connection have made IMD fast and responsive when working with systems of up to 10,000 atoms.

In the next year we intend to refine the IMD user interface to allow more sophisticated methods of user control in order to take full advantage of the extra degrees of freedom available with a 6-D input device. We will also continue to use and improve IMD's capacity as a teaching instrument for introducing scientists and laymen alike to molecular dynamics.

BTA UNIT: T

TITLE: Algorithm Development

KEYWORDS: integration methods, multiple time stepping, fast electrostatics, molecular dynamics

AXIS I: 9

AXIS II: 42, 48

INVEST1: Jesús Izaguirre
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DEPT1: Department of Computer Science
NONHOST1:

INVEST2: David Hardy
DEGREE2: M.S.
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INVEST3: Ismail Tezcan
DEGREE3: M.S.
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% BRTP $: 2%

ABSTRACT: Molecular dynamics simulations compute atomic trajectories in time increments of 1 or 2 femtoseconds with each step requiring a costly force evaluation. This project seeks to reduce computational effort in MD simulations through efficient algorithms for time stepping and force evaluation.* In particular, a multigrid algorithm has been developed for the fast evaluation of electrostatics forces in the case of nonperiodic boundaries. The method yields a continuously differentiable potential energy function. It uses a 4 by 4 by 4 stencil for interpolation. Some preliminary tests indicate that the first version of the algorithm performs as well as the fast multipole method for biomolecular dynamics. We anticipate further improvements. The multigrid method is much simpler than the fast multipole method and can be more readily integrated into the dynamics code. Also, it separates different spatial scales in a way that is most usable for multiple time stepping. The multigrid method

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

should parallelize well and this is to be tested. The method appears also to be applicable to periodic boundaries.

In the area of time integration, testing was completed for the mollified impulse method [77], which allows a 50% longer time step for long range forces. Currently under study is the use of light Langevin damping for much longer time steps.

BTA UNIT: T

TITLE: Computational Facility

KEYWORDS: parallel computing, visualization, computer networking

AXIS I: 11

AXIS II:

INVEST1: Tim Skirvin
DEGREE1: B.S.
DEPT1: Theoretical Biophysics
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% BRTP $: 5%

ABSTRACT: Over the past year the Resource has made two major changes to its computational facility: increasing the number of visualization clients and consolidating the system servers. These changes were rendered to make better use of the Resource's facilities and time.* The Resource currently has 50 local and 75 outside users.

In the past year the Resource has purchased 15 graphics workstations, which have been placed on researchers' desks for ease of access. These machines complement the 10 pre-existing public visualization workstations. Additionally, the Resource's 3D facility is being remodeled with a new server, screen, and projector, to display large visualizations for both visitors and local researchers.

On the back-end, the last year has seen the Resource's core services consolidated onto a small number of Sun servers. Approximately half a terabyte of disk space houses the Resource's data, which is distributed to about 75 clients and is backed up nightly. Services are handled by redundant servers, minimizing downtime and risk of system failure.

Computational resources remain approximately the same as last year; no new machines have been purchased. About 75% of the disk space and 90% of the CPU time are used by local users.

As in previous years, the Resource has been awarded computer time at National Science Foundation funded supercomputing sites by the National Resource Allocation Committee (NRAC): 75,000 service units at NCSA, 65,000 units at SDSC, and 102,160 units at PSC.

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

BTA UNIT: T, D

TITLE: Molecular Modeling: The Program NAMD

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

AXIS I: 9

AXIS II: 42, 89

INVEST1: James Phillips
DEGREE1: M.S.
DEPT1: Beckman Institute
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INVEST2: Robert Brunner
DEGREE2: B.S.
DEPT2: Department of Electrical and Computer Engineering
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INVEST3: David Hardy
DEGREE3: M.S.
DEPT3: Department of Computer Science
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INVEST4: Gengbin Zheng
DEGREE4: B.S.
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NONHOST4:

% BRTP $: 12%

ABSTRACT: NAMD is a parallel, object-oriented molecular dynamics code designed for high-performance simulation of large biomolecular systems [18]. NAMD 2.1 was officially released on November 11, 1999, following four beta releases during the previous two months, and has since been downloaded free of charge as binaries and/or C++ source code by over 500 registered users.*

NAMD 2.1 provides several major advantages over version 2.0. Configuration files are parsed by the interpreter of the popular Tcl scripting language, allowing end

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

users to set and access variables, include other files, and write new simulation protocols. A new interactive molecular dynamics network protocol replaces the complex and unused MDComm package; only a port number is needed to allow VMD to connect. Periodic boundary conditions are supported for non-orthogonal cells. The mollified impulse integration method reduces the required frequency of full electrostatics evaluations, and the performance of the particle mesh Ewald algorithm has been improved. NAMD 2.1 has a new license agreement and database-enabled registration system. It has been installed for general use at PSC and NCSA.

NAMD 2.2 will have its first beta release in May, 2000. User-written simulation protocols can checkpoint and revert the simulation and check molecular properties through measurement functions. Minimization has been accelerated with the conjugate gradient method. Serial algorithms and memory access patterns have been optimized. NAMD and its Converse messaging layer have been ported to the IBM SP and Windows NT. A new Charm++ load balancing framework has been incorporated and serial bottlenecks have been removed to attain a speed-up of 628 on 1024 processors of the ASCI Red.

The internal organization of NAMD has been simplified in preparation for separation into a front-end user interface and a back-end computational engine. The Molecular Dynamics Application Programming Interface (MDAPI) has been developed to allow the interchange of interfaces and engines. MDAPI is being tested and refined with a serial back-end and a minimal interface in preparation for use with NAMD.

BTA UNIT: T, D

TITLE: Molecular Visualization: The Program VMD

KEYWORDS: molecular visualization, molecular graphics, interactive simulation

AXIS I: 9

AXIS II: 42, 89

INVEST1: John Stone
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DEPT1: Beckman Institute
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INVEST2: Justin Gullingsrud
DEGREE2: B.A.
DEPT2: Department of Physics
NONHOST2:

% BRTP $: 12%

ABSTRACT: VMD [21] is an advanced molecular visualization program that provides biomolecular display and analysis capabilities. The primary development goals for VMD in the last year have been porting VMD to the Microsoft Windows, supporting 3-D positioning devices with haptic feedback, interactive molecular dynamics features, and increasing overall performance.

VMD 1.4 was released on January 7, 2000 and contains significant new features and improvements over prior verions.* Most notable of these features and improvements are:

- the port of VMD to Microsoft Windows 95/98/NT,
- Interactive Molecular Dynamics features,
- support for reading opposite-endian DCD trajectory files,
- a fast "screen door" transparency algorithm,
- elimination of CPU time consumption when the program is idle,
- a 20x speed increase when loading large molecules, and
- a 50-100x speed increase for distance-based atom selections.

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

More than 3000 users have registered and downloaded VMD 1.4, of whom 400 are NIH funded researchers. VMD 1.5 is scheduled to be released in late spring, 2000.

Future VMD development will focus on enhancing user friendliness, new isovalue surface rendering capabilities, increased web interaction, collaborative visualization features, and further enhancements to rendering performance.

BTA UNIT: C

TITLE: Mechanical Unfolding of Titin Immunoglobulin Domains

KEYWORDS: titin, folding, refolding, immunoglobulin, force, SMD

AXIS I: 13, 20

AXIS II: 74h

INVEST1: Barry Israelewitz
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DEPT1: Center for Biophysics and Computational Biology
NONHOST1:

INVEST2: Hui Lu
DEGREE2: Ph. D.
DEPT2: Physics
NONHOST2:

INVEST3: Mu Gao
DEGREE3: B.S.
DEPT3: Physics
NONHOST3:

INVEST4: Julio Fernandez
DEGREE4: Ph. D.
DEPT4: Department of Physiology and Biophsyics
NONHOST4: Mayo Clinic

% BRTP $: 2%

ABSTRACT: The modular protein titin, which is responsible for the passive elasticity of muscle, contains roughly 100 immunoglobulin (Ig) domains. Experimental elongation of single titin molecules has suggested that force causes consecutive unfolding of each Ig domain in an all-or-none fashion [78]. We have demonstrated [79], using steered molecular dynamics (SMD) [80] simulations in combination with atomic force microscopy (AFM) experiments, that a fast and reversible unfolding intermediate [61] occurs prior to full domain unfolding. Single proteins were engineered to have multiple copies of single immunoglobulin domains of human cardiac titin. Elongation

of these modules in AFM experiments demonstrated an abrupt extension of every domain by ∼7 Å prior to the first domain unfolding event. SMD simulations* showed [17,81] that the rupture of a pair of hydrogen bonds near the N-terminus of a protein domain causes a ∼6 Å extension, and suggested site-directed mutagenesis experiments that disrupted the predicted hydrogen bonds, and, indeed, eliminated the forced-unfolding intermediate in AFM observations [79].

SMD studies provided new details of the dominant peak seen in the domain unfolding force-extension graph; solvating water molecules attacking interstrand hydrogen bonds were found to be essential for the breaking of the six interstrand bonds that provide the domain its chief protection against force-induced unfolding [82]. Water molecules repeatedly interact with the protein backbone atoms, weakening individual interstrand H-bonds until all six H-bonds break simultaneously under the influence of external stretching forces.

Additional site-directed Ig domain mutants have been created to characterize the mechanical details of the main unfolding barrier. AFM extension was performed on Ig mutants designed to have fewer backbone hydrogen bonds; SMD simulations were performed on the corresponding homology-modeled structures. Other SMD simulations examined refolding of native Ig domains: domain extension was halted (applied force set to zero) immediately after a domain entered the pre-unfolding intermediate state, or after it passed the extension at which the dominant force-extension peak is observed; the simulations revealed rapid partial refolding, but did not exhibit the reformation of interstrand hydrogen bonds.

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

BTA UNIT: C

TITLE: Modeling DNA loops using the theory of elasticity

KEYWORDS: protein-DNA interactions, gene regulation, multi-resolution modeling, Kirchhoff equations

AXIS I: 2,7,9

AXIS II: 42,74g,77,89

INVEST1: Alexander Balaeff
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DEPT1: Center for Biophysics and Computational Biology
NONHOST1:

INVEST2: L. Mahadevan
DEGREE2: Professor
DEPT2: Mechanical Engineering
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% BRTP $: 2%

ABSTRACT: Protein-DNA interactions lie at the root of all cellular processes [83, 84]. Modeling the structure and dynamics of protein-DNA complexes resulting from these interactions is of enormous importance for molecular biology and biotechnology. Effective models would combine very detailed (*e.g.*, the all-atom) description of the key parts of the complexes, such as protein-DNA interfaces, with low resolution description of the other parts. For example, the DNA loops formed due to clamping of two distant DNA sites by a protein [85, 86] may be modeled as integral elastic bodies exerting certain clamping-resistance forces upon the rest of the system.

We elaborated the latter approach, following our previously developed model* [87] . The conformations of DNA loops with clamped ends are obtained as solutions to the Kirchhoff equations of elasticity [88]. The equations are augmented with electrostatic and van der Waals terms, accounting for the DNA interaction with itself and other macromolecules. The equations relate the generated DNA structure to the experimental observations through such parameters as the DNA stiffness moduli, the DNA intrinsic curvature and twist, which may vary along the DNA loop depending on the DNA sequence [89]. Together, the developed equations yield a very realistic description of DNA.

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

We applied the developed approach [87] to study the ternary complex between the *lac* repressor [90], the catabolite activator protein (CAP) [91], and a 76 bp long DNA loop. The DNA bending induced by CAP was mimicked by raising intrinsic curvature at the CAP binding cite within each of the two predicted conformations of the DNA loop clamped by the *lac* repressor [87]. It was shown that the noted cooperation of the CAP with the *lac* repressor [92] is likely to have an *entropic* mechanism: not only does the CAP favorably bind the lower energy DNA loop, but it also stabilizes the higher energy loop. The stabilization can be achieved by displacing one of the *lac* repressor headgroups by 6-8 bp upstream along the DNA, in agreement with experimental observations [93].

Our plans for the next funding year are to study the effect of the DNA sequence on the conformation of the *lac* repressor-clamped loop and to apply the developed method to study nucleosomal DNA [94, 95].

BTA UNIT: C

TITLE: Sampling of elastic conformations of DNA in Protein-DNA complexes

KEYWORDS: gene expression, elasticity, DNA conformations, Monte-Carlo sampling

AXIS I: 2, 9

AXIS II: 74g

INVEST1: Melih K. Sener
DEGREE1: Ph. D.
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INVEST2: Alexander Balaef
DEGREE2: M. S.
DEPT2: Department of Biophysics
NONHOST2:

% BRTP $: 4%

ABSTRACT: Protein-DNA interactions play a key role in transcriptional control of gene expression as well as in the replication and the storage of genetic material. In many cases the protein-DNA complex is too large for all atom molecular dynamics modeling, thus necessitating a coarser description of the DNA as provided by elasticity theory. In earlier studies we applied Kirchoff's equations of elasticity theory to locate conformational minima of a DNA loop clamped by the lac repressor [8].* We now seek to sample all possible elastic conformations realized by the DNA. This becomes especially important for longer DNA segments, where many different conformational minima are present. With the goal of a better understanding of elastic stresses on protein-DNA complexes, we are currently developing the framework for a Monte-Carlo method for sampling conformational energy minima of DNA bound by a protein.

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

BTA UNIT: C

TITLE: Purple Membrane of Halobacterium salinarium

KEYWORDS: purple membrane, bacteriorhodopsin, retinal proteins, molecular modeling

AXIS I: 7a, 9

AXIS II: 74h, 89

INVEST1: Jerome Baudry
DEGREE1: Ph.D.
DEPT1: The Beckman Institute
NONHOST1:

INVEST2: James Phillips
DEGREE2: M.S.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: Emadeddin Tajkhorshid
DEGREE3: Ph.D.
DEPT3: The Beckman Institute
NONHOST3:

% BRTP $: 5%

ABSTRACT: Electron microscopy [3] and crystallographic structures [4–6] of bacteriorhodopsin of Halobacterium salinarium associated with lipids of its native membrane, the purple membrane, were combined into a hexagonally ordered periodic structure as it exists in the bacterial cell wall [7]. The model reproduces the known stoichiometry of lipids and proteins of the purple membrane and could assign all of the ten lipids per protein, except one. For the latter lipid an empty site at the center of a bacteriorhodopsin trimer and not directly adjacent to the proteins suggested itself for placement. The resulting model, an infinite two-dimensional ordered array stacked into repetitive layers, was hydrated and then subjected to a molecular dynamics simulation employing NAMD.

The simulation [7] pressurized the elementary (hexagonal) cell that contained 23,700 atoms of protein, lipid, ion, and water components to 1 atm through adjustable cell boundaries and equilibrated the system to 300 K. After 1 ns resulted a stable geometry that differed insignificantly in the lateral directions, but exhibited a shrinking of the inter-layer distances due to a distribution of water into some inter-protein

space. A constant volume simulation of 1 ns yielded key physical characteristics of the purple membrane that are in agreement with observed properties.

Ongoing modeling work seeks to describe the photoprocess of the purple membrane and ultimately its entire function, the photo-induced pumping of protons*.

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

BTA UNIT: C

TITLE: Excitation transfer in photosynthetic light-harvesting

KEYWORDS: Effective Hamiltonian, Förster theory, carotenoids, chlorophylls

AXIS I: 7a, 9

AXIS II: 74h

INVEST1: Ana Damjanovic
DEGREE1: B.S.
DEPT1: Department of Physics
NONHOST1:

INVEST2: Thorsten Ritz
DEGREE2: B.S.
DEPT2: Department of Physics
NONHOST2:

INVEST3: Sinan Arslan
DEGREE3: B.S.
DEPT3: Department of Physics
NONHOST3:

INVEST4: Xiche Hu
DEGREE4: Ph.D.
DEPT4: Department of Chemistry
NONHOST4: University of Toledo, Ohio

% BRTP $: 1%

ABSTRACT: Photosynthetic organisms harvest the light of the sun and utilize its energy to drive chemical reactions. To harness the light, they have developed photosynthetic units (PSU's), which include thousands of chromophores [bacteriochlorophylls (Chls) and carotenoids (Cars)]. Determination of the crystal structure of the antenna light harvesting complex II [44, 45], as well as modeling of the atomic structure of light-harvesting complex I [46], which directly surrounds the photosynthetic reaction center, yields a complete picture of chromophore organization in the PSU of purple

bacteria*. This revealed a hierarchical arrangement of the above mentioned chromophores that serve to funnel the light energy, in a series of excitation transfer steps toward the photosynthetic reaction center within the PSU.

We have developed an effective Hamiltonian description of electronic excitation transfer involving systems of tightly coupled chromophores as they exist in light-harvesting complexes. Using this description, we evaluated the rates for all excitation transfer processes between Chls in purple bacteria [47, 48].

In addition, we have developed a theoretical framework to describe excitation transfer between carotenoids and chlorophylls [49]. This enabled us to identify the dominant transfer mechanism of excitation transfer, and to study the pathways of excitation transfer in all structurally known carotenoid-chlorophyll systems, namely in LH-II from *Rs. molischianum* [47], in LH-II from *Rps. acidophila*, and in PCP from *A .carterae* [48].

With the increasing number of structurally discovered proteins, the focus of biomedical research is shifting from investigating the architecture and function of individual proteins to investigate the organization and function of multi-protein molecular machineries in cells. One of these multi-component cellular machineries is the photosynthetic unit, and the present study sets a precedent for the study of cellular machines at the multi-protein level.

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

BTA UNIT: C

TITLE: Gold Binding Protein

KEYWORDS: biomineralization, gold, molecular dynamics, ab initio md

AXIS I: 2

AXIS II: 74h

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

INVEST2: Mehmet Sarikaya
DEGREE2: Ph.D.
DEPT2: Materials Science and Engineering
NONHOST2: University of Washington, Seattle

% BRTP $: 3%

ABSTRACT: The biological control of inorganic crystal morphology is necessary for the formation of biological hard tissue. Sarikaya et al. have developed a genetic system to isolate proteins which control gold crystalization. It was shown [96] 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 apparent. It is also unknown why the {111} surface would be prefered to (e.g.) the more sparsely populated {112} face. Both chemisorption (via GBP's methionine sulfurs) and physisorbtion (via polar side-chains) could play a role in the binding.

We have predicted structures for the three GBP sequences available using sequence similarity methods in addition to the Holley-Karplus prediction method [97] implemented in Quanta [98]. Of the three proteins, two are seen to have repeating motifs

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

which may be conducive to binding to a periodic surface. We have begun to carry out ab initio dynamics to study the interaction between the methionine and gold (the experimental liturature is conflicting on whether the methionine sulfur is likely to form the bond). To investigate the role of physisorbtion, we are starting molecular dynamics simulations of GBPs on both the {111} and {112} crystal surfaces, for both the case in which the methionine is bound and for which it is not. The solvated systems ($\sim$ 30000 atoms) are being simulated using NAMD [20].

BioCoRE: A Collaboratory For Structural Biology* – Supplement Award

BTA UNIT: T, D
% BRTP $: 16%

INVESTIGATORS: David Brandon, M.Sc.
Robert Brunner, Ph.D.
Jayant DeSouza, M.Sc.
Sameer Kumar, B.A.
Kirby Vandivort M.Sc.
Hui Wang, M.Sc.
Jeffrey Wright, B.A.

Overview

In the past year the Resource has continued development of BioCoRE (*Bio*logical *Co*llaborative *R*esearch *E*nvironment). BioCoRE is funded through an NIH supplemental award to establish a testbed designed to facilitate collaborative work between biomedical researchers located at the same or geographically distant sites.

BioCoRE is being developed to support 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 effectiveness of the new environment.

Progress in the past year

Technical

The initial version of BioCoRE was released to the public on March 1st of this year, and already supports three of the four activity areas specified above: *Workbench*, *Notebook*, and *Conferences*. Members of the Resource are currently evaluating the *Documents* component to find the best ways to implement it. For the *Workbench* component, BioCoRE allows researchers (initially Resource members; soon researchers from anywhere) to submit and monitor computational jobs via a web interface (see Fig. 5). In addition, researchers can use the BioCoRE interface to start VMD† sessions on their local machines.

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

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

The *Notebook* component furnishes researchers with an offline forum to discuss topics and browse recordings of previous conference sessions. The *Conferences* component currently includes on-line text chat sessions, which are saved in the notebook at the conclusion of the chat for future review.

The BioCoRE programming team has decided, following extensive discussions and survey of available and anticipated technologies on the market, to implement BioCoRE as a collection of Java servlets that output standard HTML. The servlets mostly abide by Java 1.1 specifications, with some use of Java 1.2. BioCoRE uses version 2.0 of the JSDK (Java Servlet Development Kit) and the Apache webserver (version 1.3.12) with JServ version 1.1. The OpenSSL module available for Apache provides secure connections (via SSL/https).

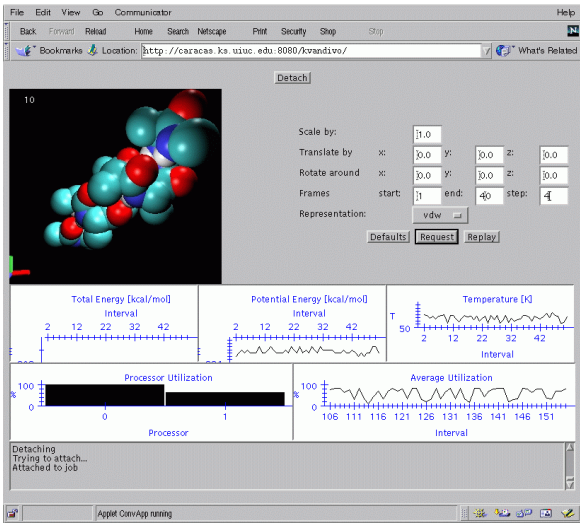

Figure 5: The interface to the simulation monitoring tool, showing views of the molecule being simulated and continuously updated graphs of the simulation status

The simulation monitoring tool, a major component of the workbench in the first released version, requires more flexibility than pure HTML would allow and, therefore, has been implemented as a Java applet. Similarly, the process of starting VMD from the web browser also requires a high level of flexibility and is done using a Java applet and security certificate (to allow execution of processes on the browser's machine). As the components grow more sophisticated, BioCoRE will likely move to more Java applets.

Licensing and Registration

The BioCoRE registration process is simple and user-friendly. The usage license is flexible and places minimal requirements on the user. When prospective users visit the BioCoRE website for the first time, they are presented with the BioCoRE license. Then, they are informed of the built-in evaluation component and are asked to review the evaluation

guidelines. New users must agree to have their actions monitored if they wish to use BioCoRE. Once they have agreed, they are asked to complete a registration form providing information about their identity, affiliation, and basic research needs. After this first-time registration process the users use a username/password combination to gain regular access to BioCoRE.

All of the user's data is stored in a database (MySQL) and the JDBC is being used to communicate between the Java servlets and the database. While a user is logged onto BioCoRE, a non-persistent cookie consisting of a single integer number is stored on the user's computer. This cookie (along with a lookup table in the database) is used by the java servlets to identify the user.

Distribution and Support

The BioCoRE environment is available free of charge on the Resource's computers. Users can visit the Resource's website and work with BioCoRE without needing to download or install any software. (However, if they want to launch VMD from BioCoRE they would need to download and install VMD on their computer.) This method of software distribution allows the BioCoRE team to release regular and frequent updates. The developers have time allocated each week to perform BioCoRE upgrades and as a result users are not forced to wait for a major release to start benefitting from new additions to the collaboratory. As of April 18, 2000, 88 people have registered to use BioCoRE, collaborating on projects involving biophysics training, joint document preparation, and molecular function.

The Resource's goal is to be as responsive as possible to users' requests. Once a problem is identified, the developers typically fix it and respond to the user within 24 hours. The Resource has set up an e-mail address that users can send problems to, which allows any person on the development team to answer rapidly. Additionally, the Resource has also set up a web-based feedback form that users can fill out; the feedback data are stored in a database which can be searched and filtered to obtain additional information.

Evaluation

The BioCoRE development relies on standards of computer science research, knowledge of technological developments in academia and industry, as well as users needs, and expectations. The Resource is seeking a successful marriage between sound computer science solutions and users' expectations and needs.

A key evaluation goal is to offer the developers the correcting mechanism that would keep them on track. The evaluation component focuses on the users and is two-fold:

- assessing the software through the eyes, voice, and actions of the users;
- bringing the users closer to the developers and have them contribute to the development process;

Funding agency requirements and the Resource's own experience and convictions have led us to design an evaluation process as detailed and as comprehensive as possible, with a strong emphasis on use of all tools available for that purpose. Having the evaluation tools as a built-in component of the collaboratory allows us to

1. take advantage of the cutting edge technologies used by the development team;
2. work as closely as possible with the development team and get their immediate feedback on all evaluation related matters and ideas;
3. keep the development team constantly and thoroughly informed of users' concerns, difficulties and needs.

The evaluation team is collecting systematic information on BioCoRE users, and the data can be classified into two basic categories:

1. Process data
    - user-tool interactions
    - user-user interactions (notebook and chat rooms)
    - tool-tool interactions
    - users' questions, support calls, bug reports, and other comments
    - interviews (face-to-face, telephone)
    - surveys and feedback forms which are designed to generate relevant biodata on the users, identify research interests, expectations, views on collaborations, satisfaction, and experience
2. Outcome Data
    - users' satisfaction
    - attrition, commitment, involvement
    - number of resulting publications in refereed journals
    - citations of resulting work
    - professional progress of participants

- funding resources
- other established indicators

All users' information collected, qualitative and quantitative, is stored in a database. The quantitative data feed back into data summary pages in real-time. The page provides clearly formatted resulting statistics (by survey item, by respondent group, by any defined variable that is part of the evaluation design).

The data collection and related tools already implemented are web-based and include

- pre-interviews of UIUC collaborators (main topics covered: collaborative work practices and preferences such as choice of collaboration; defining joint goals; competition/cooperation; communication patterns and effectiveness; documentation and keeping track of each others progress; mutual trust; interdependency)
- registration form
- consent form
- long interviews of off-campus collaborators
- quick interviews of TB users
- feedback form and data summary form
- bi-annual users' interviews

Content, functionality and design all have a role in developing the tools. The very fundamental desire *not* to annoy the users is always in the minds of the evaluation team. The Resource is painfully aware of the fine line it is treading: on the one hand it must establish trust, loyalty and commitment by integrating the users into the process, on the other hand the Resource must prevent any feeling on the users' part that they are being pushed into doing something they neither need nor want.

Personnel

Presently the Resource has three full-time research programmers working on the project. In addition, the Resource has had two computer science graduate research assistants assigned to the project and a social science student working with the team since summer, 1999.

New Hardware

In April 2000, the Resource acquired a dual processor Sun E250 to serve as the main collaboratory server. The E250 has 2 gigabytes of RAM and 18 gigabytes of storage available. This machine is expected to fulfill BioCoRE's needs into the foreseeable future.

Dissemination

The BioCoRE team has been engaged this past year in extensive dissemination efforts.

The Resource has given seven on-site private demonstrations to on-campus researchers, such as Larry Smarr (NCSA Director) and Jiri Jonas (Beckman Director), as well as to off-campus visitors (including Michael McRobbie, CIO, Indiana U. system; Roscoe Giles, Boston U.; Angela Gronenborn, NIH Lab of Chemical Physics). Resource members have also given a number of public talks and demonstrations including SC99[‡] in Portland, Oregon, the Beckman Institute Open House[§], the Parallel MD Development and Use conference[¶], a Beckman Institute Imaging Technology Group forum[‖], and a poster demonstration at the HICS conference at the Beckman Institute[**].

Over the past year the BioCoRE website has been fully integrated into the Resource website, in terms of design and structure. Since the release on March 1, the webpages have enjoyed increased traffic. (From April 29, 1999 through February 29, 2000 the Resource had 749 accesses to the main BioCoRE page from non-Resource machines, an average of about 2.5 accesses per day. From March 1, 2000 - April 12, 2000 the Resource had 1555 accesses to the same page from non-Resource machines, an average of about 47 accesses per day.

Key plans for the next 12 months

Over the next twelve months the BioCoRE team plans on refining the existing tools (such as the chat rooms and the notebook) and increasing their functionality and user-friendliness, as well as focusing on tighter integration with 3rd party programs in structural biology. The Resource plans to make the job submission tool more versatile by

[‡]URL: `http://www.ks.uiuc.edu/Research/biocore/presentations/sc99.shtml`

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

[¶]URL: `http://www.ks.uiuc.edu/Services/Meetings_Tutorials/Meetings/ParallelMD/`

[‖]URL: `http://www.itg.uiuc.edu/forums/`

[**]URL: `http://www.beckman.uiuc.edu/outreach/HICS2000`

extending its usefulness beyond users affiliated with the Resource. The development team also intends to have the BioCoRE source code in a state that can be distributed to other researchers (while still insuring that we retrieve the evaluation data needed to complete that part of the project).

	TECH RES & DEVEL (T)	COLLAB RES & SERVICE (C)	DISSEM & TRAINING (D)	TOTALS
NUMBER OF PUBLICATIONS	17	16	—	33
NUMBER OF SUBPROJECTS	16	6	3	25*
NUMBER OF INVESTIGATORS	32	17	6	55*
PERCENT OF BRTP FUNDS ALLOCATED	67%	17%	16%	100%
SERVICE FEES COLLECTED	0	0	0	0
OTHER FUNDS ($)	150,000	200,000	—	350,000

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

State or Country	Number of Investigators
IL	31
WA	1
CA	1
MA	1
MN	1
IN	1
OH	1

BRTP Unit T

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Ben-Nun, Michal	University of Illinois (Martinez, Todd)	FED	NIH
Brandon, David	University of Illinois (Budescu, Gila)	FED	NIH
Bruinsma, Robijn	UCLA, CA (Bruinsma, Robijn)	FED	NSF
Brunner, Robert	University of Illinois (Kale, Laximkant)	FED	NIH
DeSouza, Jayant	University of Illinois (Kale, Laximkant)	FED	NIH
Gullingsrud, Justin	University of Illinois (Schulten, Klaus)	FED	NIH
Hardy David	University of Illinois (Skeel, Robert)	OTH	
Izaguirre, Jesús	University of Illinois (Skeel, Robert)	FED	NSF
Kosztin Dorina	University of Illinois (Schulten, Klaus)	OTH	
Kosztin, Ioan	University of Illinois (Schulten, Klaus)	OTH/FED	NIH
Kumar, Sameer	University of Illinois (Kale, Laximkant)	FED	NIH
Molnar, Ferenc	University of Illinois (Schulten, Klaus)	FED	NIH/NSF
Moore, D. B.	University of Illinois (Moore, D. B.)	FED	NIH
Phillips, James	University of Illinois (Schulten, Klaus)	FED	DOE
Phillips, John B.	Indiana University, IN (Phillips, John B.)	FED	NSF

continued on next page

continued from previous page			
Investigator	**Non-Host Institution (Principal Investigator)**	**Sources of Support**	
		TYPE	**AGENCY**
Ritz, Thorsten	University of Illinois (Schulten, Klaus)	OTH	
Skirvin, Tim	University of Illinois (Schulten, Klaus)	FED	NIH
Stone, John	University of Illinois (Schulten, Klaus)	FED	NIH
Tezcan Ismail	University of Illinois (Schulten, Klaus)	OTH	
Vandivort, Kirby	University of Illinois (Schulten, Klaus)	FED	NIH
Wang, Hui	University of Illinois (Schulten, Klaus)	FED	NIH
Wright, Jeffrey	University of Illinois (Kale, Laximkant)	FED	NIH
Zheng, Gengbin	University of Illinois (Kale, Laximkant)	FED	NIH

BRTP Unit C

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Arslan, Sinan	University of Illinois (Schulten, Klaus)	OTH	
Balaeff, Alexander	University of Illinois (Schulten, Klaus)	OTH	
Baudry, Jerome	University of Illinois (Schulten, Klaus)	FED	NSF/NIH
Braun, Rosemary	University of Illinois (Schulten, Klaus)	OTH	
Damjanovic, Ana	University of Illinois (Schulten, Klaus)	OTH	
Fernandez, Julio	Mayo Clinic (Fernandez, Julio)	FED	NIH
Gao, Mu	University of Illinois (Schulten, Klaus)	OTH	
Hu, Xiche	University of Toledo, OH (Hu, Xiche)	OTH	
Isralewitz, Barry	University of Illinois (Schulten, Klaus)	OTH	
Lu, Hui	University of Illinois (Schulten, Klaus)	FED	NSF
Mahadevan. L	MIT, MA (Mahadevan. L)	FED	NIH
Phillips, James	University of Illinois (Schulten, Klaus)	FED	NIH
Ritz, Thorsten	University of Illinois (Schulten, Klaus)	OTH	
Sarikaya, Mehmet	University of Washington, Seattle (Sarikaya, Mehmet)	FED	NIH/NSF
Sener Melih	University of Illinois (Schulten, Klaus)	FED	NIH
Tajkhorshid, Emadeddin	University of Illinois (Schulten, Klaus)	FED	NIH

BRTP Unit D

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Brandon, David	University of Illinois (Budescu, Gila)	FED	NIH
Brunner, Robert	University of Illinois (Kale, Laximkant)	FED	NIH
Hardy, David	University of Illinois (Skeel, Robert)	OTH	
DeSouza, Jayant	University of Illinois (Kale, Laximkant)	FED	NIH
Gullingsrud, Justin	University of Illinois (Schulten, Klaus)	FED	NIH
Kumar, Sameer	University of Illinois (Kale, Laximkant)	FED	NIH
Phillips, James	University of Illinois (Schulten, Klaus)	FED	NIH
Stone, John	University of Illinois (Schulten, Klaus)	FED	NIH
Vandivort, Kirby	University of Illinois (Schulten, Klaus)	FED	NIH
Wang, Hui	University of Illinois (Schulten, Klaus)	FED	NIH
Wright, Jeffrey	University of Illinois (Kale, Laximkant)	FED	NIH
Zheng, Gengbin	University of Illinois (Kale, Laximkant)	FED	NIH

BTA unit: (T)

NUMBER PUBLISHED –
Books: 0 Papers: 12 Abstracts: 0

NUMBER IN PRESS OR SUBMITTED –
Books: 0 Papers: 5 Abstracts: 0

Books:
None

Papers
Published: 12

1. M. Ben-nun and T. J. Martínez. Electronic absorption and resonance raman spectroscopy from ab initio quantum molecular dynamics. *J. Phys. Chem. A*, 103(49):10517–10527, 1999.

2. M. Ben-nun and T. J. Martínez. Exploiting temporal non-locality to remove scaling bottlenecks in non-adiabatic quantum dynamics. *J. Chem. Phys.*, 110:4134, 1999.

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Abstracts:
None

BTA unit: (C)

NUMBER PUBLISHED –
Books: 0 Papers: 9 Abstracts: 0

NUMBER IN PRESS OR SUBMITTED –
Books: 0 Papers: 7 Abstracts: 0

Books:
None

Papers
Published: 9

1. A. Balaeff, L. Mahadevan, and K. Schulten. Elastic rod model of a DNA loop in the lac operon. *Physical Review Letters*, 83:4900–4903, 1999.

2. A. Damjanovic, T. Ritz, and K. Schulten. Excitation energy trapping by the reaction center of Rhodobacter sphaeroides. *Int. J. Quantum Chem.*, 77:139–151, 2000.

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1. H. Lu, A. Krammer, B. Isralewitz, V. Vogel, and K. Schulten. Computer modeling of force-induced titin domain unfolding. In Jerry Pollack and Henk Granzier, editors, *Elastic Filaments of the Cell*, chapter 1. Kluwer Academic/Plenum Publishers, New York, NY, In Press, 1999.

2. H. Lu and K. Schulten. The key event in force-induced unfolding of titin's immunoglobulin domains. *Biophysical Journal*, In Press, 2000.

3. J. Baudry, E. Tajkhorshid, F. Molnar, J. Phillips, and K. Schulten. Molecular Dynamics Study of Bacteriorhodopsin and the Purple Membrane. *J. Phys. Chem.*, Submitted, 2000.

4. A. Damjanovic, T. Ritz, and K. Schulten. Excitation Energy Transfer in the Peridinin-Chlorophyll-Protein of Amphidinum carterae. *Biophysical Journal*, Submitted, 1999.

5. A. Kessel, K. Schulten, and N. Ben-Tal. Calculations Suggest a Pathway for the Transmembrane Migration of a Hydrophobic Peptide. *Biophysical Journal*, Submitted, 2000.

6. F. Molnar, L. S. Norris, and K. Schulten. Simulated Unbinding and Arachidonic Acid in the Cyclooxygenase Site of Prostaglandin H2 Synthase-1. *Reaction Kinetics & Mechanisms*, Submitted, 2000.

7. T. Ritz, A. Damjanovic, K. Schulten, J-P. Zhang and Y. Koyama. Efficient Light Harvesting Through Carotenoids. *Photosynthesis Research*, Submitted, 2000.

Abstracts:
None

BTA unit: (D)

NUMBER PUBLISHED –
Books: 0 Papers: 0 Abstracts: 0

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

Books:
None

Papers:
None

Abstracts:
None

Web Documents:

Advisory Committee

The recent Advisory board meeting was on 9/16/99 (see attached agenda) In our ongoing efforts to ensure a close fit between the research and development areas of the Resource and the expertise of the board members, two of the previous members retired and new members agreed to join. Attila Szabo and Bernie Alder who served for many years on our board, and skillfully guided us with their expert advice, have now retired from the advisory board. The members of our renewed advisory board are:

- Biophysics - Harel Weinstein, Mount Sinai School of Medicine
- Biophysics - Colin Wraight, School of Life Sciences, UIUC
- Structural Biology - Joel Berendzen, Physics Division, LANL
- Biocomputing - Bernie Brooks,Computational Research and Technology, NIH
- Bioinformatics - Jeff Skolnick, Scripps Research Institute
- Computer Science - Dannis Gannon, Computer Science, IU
- Mathematics and Scientific Administration - Peter Arzberger, Advanced Scientific Computing, SDSC

A report is due soon.

The next meeting at C-U is planned for Fall 2000 .

Service, Training and Dissemination

The Resource's service, training and dissemination areas experienced a highly productive and dynamic year as is evident from the various activities reported below. As always, we have been exploring, and whenever feasible exploiting, all relevant avenues to expand and fortify these functions. The newly released BioCoRE environment further strengthens the Resource's capacity to offer quality and broadly defined service to the structural biology community.

In the past year the Resource has substantially increased the size of our scientific and technical support staff. A new Assistant Director for Research was recruited to assist the PI in advising students and guiding their research activities. With two new full time programmers, who joined the Resource in the fall of 1999 and the spring of 2000, the Resource has established a cohesive and dedicated team of five highly qualified programmers ready to fully attain the Resource's software development aspirations across VMD, NAMD and BioCoRE. A skilled system administrator has recently joined the Resource and will ensure the professional support of the cutting edge technology needed to meet the research and development targets.

Service

The services offered by the Resource are enjoyed by a vast number of biomedical researchers, domestic and international. A large fraction of the Resource's user population is directly involved with medical research sponsored by the National Institutes of Health (NIH). An estimated 15% of the Resource's software users (VMD, NAMD and BioCoRE) are NIH supported. Much of the work citing VMD and NAMD is by researchers funded by NIH. Several of the Resource's experimental collaborators are recipients of NIH grants as are speakers invited to participate in the Resource's regular seminar series. Moreover, many in the UIUC audience attending the seminars receive NIH support. Last but not least, the meeting Parallel MD Development and Use — Challenges and Opportunities, organized by the Resource on April 16-17 of this year, brought together world-class biomedical researchers, many of whom are supported by NIH. Details on each of these service endeavors are outlined below.

The services the Resource offers may be classified into two broad categories:

- Technological services, designed to provide the scientific community with easy access to and use of the Resource's and others' software and hardware technology;
- General services which focus on creating new collaborations, sharing the knowledge and expertise produced by existing collaborations, and ongoing application projects with other biomedical scientists.

Technological Service The technological area has accomplished far-reaching goals in the past year, the most prominent are the new versions of VMD and NAMD and the brand new release of BioCoRE. Along the way, the programming team adopted cutting edge technologies that enforce the sharing of information and other resources across all projects, and bring the users closer to the developers on a daily basis, and facilitate an effective management of the entire area. The new tools include read-only CVS access, web-based publically available bug tracking for all software projects, a shared users database, sister registration procedures and licenses, and structured feedback forms. Both NAMD and VMD were ported to machines at NCSA, PSC and SDSC and are now available for these centers' users in a much more convenient manner than ever before. A special solution was implemented in order to enable the tracking of off-site users.

VMD 1.4 for Windows was released on January 7th, 2000. This most recent version of VMD contains many significant improvements over VMD 1.3:

- New 3-D tracker subsystem
- Support for haptic force feedback devices
- New Interactive Molecular Dynamics features
- Performance increase of 20 times when loading molecular systems with more than one hundred thousand atoms
- Performance increase of 50 to 100 times when performing distance-based atom selections on very large molecular systems
- Eliminated consumption of CPU time when VMD is otherwise idle
- Implemented transparency rendering feature for the OpenGL versions of VMD
- New low-level graphics display list system for increased performance and portability
- New support for several Gromos and Gromacs file formats
- Improved quality of externally rendered output files (Raster3D, POV-Ray, Radiance, Tachyon, Rayshade)

VMD has been ported to Microsoft Windows 95/98/NT and has been installed at NCSA where it can now be used as a standard CAVE application. In fact, porting VMD to Windows has been the main objective this year. The resulting increase in the number and diversity (by platform, by field, by needs) of VMD users has also provided the VMD developers with much feedback, helping to track down and eliminate software bugs. The new bug tracking tool as well as the use of the new database and better evaluation tools

have all improved the quality and scope of users information available to the developers and have brought the users and developers closer together.

VMD talks in the past year included:

- Notre Dame, April 20th, 2000 Title: "VMD – High Performance Molecular Visualization"
- University of Missouri-Rolla, April 18th, 2000 Title: "VMD – High Performance Molecular Visualization"

129 VMD demos were given upon request at the Resource and NCSA in the last year.

A VMD user survey is scheduled to start in May 2000.

Key VMD improvements planned for the next year include:

- Release of VMD 1.5 in May 2000
- New surface rendering features
- Built-in support for rendering of isovalue surfaces of volumetric data
- Increased web integration
- Integration of structure/trajectory database query capabilities
- BioCoRE event monitoring features
- BioCoRE "publish state" feature for collaborative VMD sessions
- BioCoRE control and interaction with VMD through network sockets
- Multithreading of key parts of VMD for increased performance
- Improved quality of several frequently used molecular representations
- VMD applet

A citation index search produced 43 publications that acknowledged VMD use in the past year:

1. D. B. Moore and T. J. Martinez. Ab initio study of coupled electron transfer/proton transfer in cytochrome c oxidase. *J. Phys. Chem. A*, 104(11):2367–2374, 2000.

2. M. Fujinaga, M. M. Cherney, N. I. Tarasova, P. A. Bartlett, J. E. Hanson, and M. N. G. James. Structural study of the complex between human pepsin and a phosphorus-containing peptidic transition-state analog. *Acta Crystallogr. Sect. D-Biol. Crystallogr.*, 56(11):272–279, 2000.

3. U. Reidt, K. Reuter, T. Achsel, D. Ingelfinger, R. Luhrmann, and R. Ficner. Crystal structure of the human u4/u6 small nuclear ribonucleoprotein particle-specific snucyp-20, a nuclear cyclophilin. *J. Biol. Chem.*, 275(11):7439–7442, 2000.

4. A. Anderson and Z. P. Weng. Vrdd: Applying virtual reality visualization to protein docking and design. *J. Mol. Graph.*, 17(3-4):180–+, 1999.

5. K. Nacro, B. Bienfait, J. Lee, K. C. Han, J. H. Kang, S. Benzaria, N. E. Lewin, D. K. Bhattacharyya, P. M. Blumberg, and V. E. Marquez. Conformationally constrained analogues of diacylglycerol (dag). 16. how much structural complexity is necessary for recognition and high binding affinity to protein kinase c? *J. Med. Chem.*, 43(5):921–944, 2000.

6. A. Henriksen, U. Anthoni, T. H. Nielsen, J. Sorensen, C. Christophersen, and M. Gajhede. Cyclic lipoundecapeptide tensin from pseudomonas fluorescens strain 96.578. *Acta Crystallogr. Sect. C-Cryst. Struct. Commun.*, 56(5):113–115, 2000.

7. S. M. Patra and S. Vishveshwara. Backbone cluster identification in proteins by a graph theoretical method. *Biophys. Chem.*, 84(1):13–25, 2000.

8. D. R. Bevan, L. P. Li, L. G. Pedersen, and T. A. Darden. Molecular dynamics simulations of the d(ccaacgttgg)(2) decamer: Influence of the crystal environment. *Biophys. J.*, 78(2):668–682, 2000.

9. A. Damjanovic, T. Ritz, and K. Schulten. Excitation energy trapping by the reaction center of rhodobacter sphaeroides. *Int. J. Quantum Chem.*, 77(1):139–151, 2000.

10. I. Z. Zubrzycki, Y. Xu, M. Madrid, and P. Tang. Molecular dynamics simulations of a fully hydrated dimyristoylphosphatidylcholine membrane in liquid-crystalline phase. *J. Chem. Phys.*, 112(7):3437–3441, 2000.

11. P. R. Kumar, S. Eswaramoorthy, P. J. Vithayathil, and M. A. Viswamitra. The tertiary structure at 1.59 angstrom resolution and the proposed amino acid sequence of a family-11 xylanase from the thermophilic fungus paecilomyces varioti bainier. *J. Mol. Biol.*, 295(3):581–593, 2000.

12. M. Aoudia, A. B. Guliaev, N. B. Leontis, and M. A. J. Rodgers. Self-assembled complexes of oligopeptides and metalloporphyrins: measurements of the reorganization

and electronic interaction energies for photoinduced electron- transfer reactions. *Biophys. Chem.*, 83(2):121–140, 2000.

13. K. Hinsen. The molecular modeling toolkit: A new approach to molecular simulations. *J. Comput. Chem.*, 21(2):79–85, 2000.

14. F. V. Murphy, R. M. Sweet, and M. E. A. Churchill. The structure of a chromosomal high mobility group protein-dna complex reveals sequence-neutral mechanisms important for non- sequence-specific dna recognition. *Embo J.*, 18(23):6610–6618, 1999.

15. C. F. Bleczinski and C. Richert. Steroid-dna interactions increasing stability, sequence-selectivity, dna/rna discrimination, and hypochromicity of oligonucleotide duplexes. *J. Am. Chem. Soc.*, 121(47):10889–10894, 1999.

16. Y. Xu, D. Xu, O. H. Crawford, J. R. Einstein, F. Larimer, E. Uberbacher, M. A. Unseren, and G. Zhang. Protein threading by prospect: a prediction experiment in casp3. *Protein Eng.*, 12(11):899–907, 1999.

17. A. B. Guliaev and N. B. Leontis. Cationic 5,10,15,20-tetrakis(n-methylpyridinium-4-yl)porphyrin fully intercalates at 5 '-cg-3 ' steps of duplex dna in solution. *Biochemistry*, 38(47):15425–15437, 1999.

18. J. F. W. Petersen, M. M. Cherney, H. D. Liebig, T. Skern, E. Kuechler, and M. N. G. James. The structure of the 2a proteinase from a common cold virus: a proteinase responsible for the shut-off of host-cell protein synthesis. *Embo J.*, 18(20):5463–5475, 1999.

19. T. Kakitani, Y. Beppu, and A. Yamada. Color tuning mechanism of human red and green visual pigments. *Photochem. Photobiol.*, 70(4):686–693, 1999.

20. S. Izrailev, A. R. Crofts, E. A. Berry, and K. Schulten. Steered molecular dynamics simulation of the rieske subunit motion in the cytochrome bc(1) complex. *Biophys. J.*, 77(4):1753–1768, 1999.

21. W. C. Ho, C. Steinbeck, and C. Richert. Solution structure of the aminoacyl-capped oligodeoxyribonucleotide duplex (w-tgcgcac)(2). *Biochemistry*, 38(39):12597–12606, 1999.

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26. J. R. Bamburg, A. Mcgough, and S. Ono. Putting a new twist on actin: Adf/cofilins modulate actin dynamics. *Trends Cell Biol.*, 9(9):364–370, 1999.

27. J. Zeng and H. R. Treutlein. A method for computational combinatorial peptide design of inhibitors of ras protein. *Protein Eng.*, 12(6):457–468, 1999.

28. J. F. Prins, J. Hermans, G. Mann, L. S. Nyland, and M. Simons. A virtual environment for steered molecular dynamics. *Futur. Gener. Comp. Syst.*, 15(4):485–495, 1999.

29. L. Guidoni, V. Torre, and P. Carloni. Potassium and sodium binding to the outer mouth of the k+ channel. *Biochemistry*, 38(27):8599–8604, 1999.

30. E. C. Sherer, S. A. Harris, R. Soliva, H. Orozco, and C. A. Laughton. Molecular dynamics studies of dna a-tract structure and flexibility. *J. Am. Chem. Soc.*, 121(25):5981–5991, 1999.

31. S. Krishna, C. N. Hiremath, S. K. Munshi, D. Prahadeeswaran, M. Sastri, H. S. Savithri, and M. R. N. Murthy. Three-dimensional structure of physalis mottle virus: Implications for the viral assembly. *J. Mol. Biol.*, 289(4):919–934, 1999.

32. O. Roche, K. Hinsen, and M. J. Field. Theoretical study of the conformation of the h-protein lipoamide arm as a function of its terminal group. *Proteins*, 36(2):228–237, 1999.

33. D. Barsky, E. T. Kool, and M. E. Colvin. Interaction and solvation energies of nonpolar dna base analogues and their role in polymerase insertion fidelity. *J. Biomol. Struct. Dyn.*, 16(6):1119–1134, 1999.

34. H. Lu and K. Schulten. Steered molecular dynamics simulations of force-induced protein domain unfolding. *Proteins*, 35(4):453–463, 1999.

35. O. Roche and M. J. Field. Simulations of the t ¡-¿ r conformational transition in aspartate transcarbamylase. *Protein Eng.*, 12(4):285–295, 1999.

36. A. T. Bouthors, J. Delettre, P. Mugnier, V. Jarlier, and W. Sougakoff. Site-directed mutagenesis of residues 164, 170, 171, 179, 220, 237 and 242 in per-1 beta-lactamase hydrolysing expanded- spectrum cephalosporins. *Protein Eng.*, 12(4):313–318, 1999.

37. W. Wriggers, R. A. Milligan, and J. A. Mccammon. Situs: A package for docking crystal structures into low- resolution maps from electron microscopy. *J. Struct. Biol.*, 125(2-3):185–195, 1999.

38. H. Ying, P. Y. Yang, X. R. Wang, and B. L. Huang. Virtual reality in chemistry and prospects for its application in spectrochemistry. *Chin. J. Anal. Chem.*, 27(3):354–360, 1999.

39. T. Schlick, R. D. Skeel, A. T. Brunger, L. V. Kale, J. A. Board, J. Hermans, and K. Schulten. Algorithmic challenges in computational molecular biophysics. *J. Comput. Phys.*, 151(1):9–48, 1999.

40. L. Kale, R. Skeel, M. Bhandarkar, R. Brunner, A. Gursoy, N. Krawetz, J. Phillips, A. Shinozaki, K. Varadarajan, and K. Schulten. Namd2: Greater scalability for parallel molecular dynamics. *J. Comput. Phys.*, 151(1):283–312, 1999.

41. V. Helms, T. P. Straatsma, and J. A. Mccammon. Internal dynamics of green fluorescent protein. *J. Phys. Chem. B*, 103(16):3263–3269, 1999.

42. J. Baudry, S. Crouzy, B. Roux, and J. C. Smith. Simulation analysis of the retinal conformational equilibrium in dark-adapted bacteriorhodopsin. *Biophys. J.*, 76(4):1909–1917, 1999.

43. W. Wriggers and K. Schulten. Investigating a back door mechanism of actin phosphate release by steered molecular dynamics. *Proteins*, 35(2):262–273, 1999.

NAMD 2.1 was released in November 1999. Key new features include:

- Tcl scripting language interface and config file parsing.
- Mollified impulse multiple timestepping method.
- Faster particle mesh Ewald implementation.
- Periodic boundaries for non-orthogonal cells.
- New interactive molecular dynamics interface to VMD.

NAMD 2.2 is about to be released in May 2000 with the following additional improvements:

- New checkpoint, revert, and measure Tcl commands.
- Conjugate gradient algorithm for faster minimization.
- Improved serial performance and cache utilization.
- New load balancing framework for better parallel scaling.

There are an estimated 543 NAMD 2.1 users, 81 of whom are NIH funded (15%). On the average the NAMD section in the Resource's web site was accessed 11,500/month in the past 12 months.

Key features planned for the next 12 months include:

- Improved parallelization for particle mesh Ewald
- License to ship binaries containing FFTW for parallel FFT
- Support for Myrinet NT cluster at NCSA
- Better performance on clusters of multiprocessor machines
- Modular front-end interface using MDAPI library
- Ability to generate structures without CHARMM or X-PLOR
- Ability to read AMBER force field and molecule file formats
- Support for non-physical methods such as LES and mutational FEP

NAMD talks given in the past year include:

- April 16, 2000: James Phillips, Modern Software Development Techniques in NAMD Beckman Institute, Urbana, IL
- April 16, 2000: Laxmikant Kale, Scalability and Interoperable Libraries in NAMD Beckman Institute, Urbana, IL

A citation index search produced the following publications that acknowledged NAMD use in the past year:

1. M. T. Heath and W. A. Dick. Virtual prototyping of solid propellant rockets. *Comput. Sci. Eng.*, 2(2):21–32, 2000.
2. Z. Bryant, V. S. Pande, and D. S. Rokhsar. Mechanical unfolding of a beta-hairpin using molecular dynamics. *Biophys. J.*, 78(2):584–589, 2000.

3. I. Z. Zubrzycki, Y. Xu, M. Madrid, and P. Tang. Molecular dynamics simulations of a fully hydrated dimyristoylphosphatidylcholine membrane in liquid-crystalline phase. *J. Chem. Phys.*, 112(7):3437–3441, 2000.

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7. J. A. Izaguirre, S. Reich, and R. D. Skeel. Longer time steps for molecular dynamics. *J. Chem. Phys.*, 110(20):9853–9864, 1999.

8. T. Schlick, R. D. Skeel, A. T. Brunger, L. V. Kale, J. A. Board, J. Hermans, and K. Schulten. Algorithmic challenges in computational molecular biophysics. *J. Comput. Phys.*, 151(1):9–48, 1999.

The Resource's computational facility currently has a total of 125 users: 50 local active users and 75 outside users.*

To meet the users' needs, the Resource has added 10 new cost-effective graphics machines, increasing total visualization capability by 150% over the previous year.

The Resource has hosted visitors from collaborative groups and others in the past funding period. Recent visitors include:

- Professor Robijn Bruinsma, UCLA (Winter 2000)
- Felix Autenrieth, University Stuttgart, Germany (Summer and Fall 99)
- Dr. Emadeddin Tajkhorshid, German Cancer Research Center, Heidelberg University (Summer 99)
- David Craig, U of Washington (Summer 99)
- Professor Attila Gursoy, Bilkent University, Ankara, Turkey (Summer 99)

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

General Services 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. Fifteen scientists in the field of computational structural biology were invited to discuss relevant development directions and research needs that will evolve in tandem with the anticipated increase of computer power. The key areas explored in the meeting included parallel algorithms, scalability and benchmarking and implementation issues.

See Appendix D for the summary of the workshop (agenda and abstracts of talk).

The Resource has, again, organized a highly regarded seminar series bridging the fields of biology and physics with the support of the Beckman Institute and NIH Resource funds. These seminars have become a recognized staple of UIUC campus life, constituting an effective and beneficial tradition for technology transfer and sharing of knowledge with Beckman and other on-campus scientists.

During the past year the following outside speakers have presented lectures in the Resource seminar series at the Beckman Institute:

- June 7, 1999: Willy Wriggers, Department of Chemistry and Biochemistry, UCSD, "Structure and Dynamics of Proteins and Macromolecular Assemblies Revealed by Signal Processing of Multi-Resolution Data"
- July 20, 1999: Achi Brandt, Weizmann Institute of Science, Rehovot, Israel, "Review of Multiscale Scientific Computation Methods"
- July 21, 1999: Achi Brandt, Weizmann Institute of Science, Rehovot, Israel, "Multiscale Molecular Dynamics"
- August 6, 1999: Sergei Izrailev, 3-Dimensional Pharmaceuticals, Exton, Pa, "A Novel Method of Building Regression Tree Models for Quantitative Structure-Activity Relationships (QSAR)"
- September 13, 1999: Mair Churchill, University of Colorado Health Sciences Center, Denver, CO, "Structure and Function of Chromosomal High Mobility Group Proteins"

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

- September 27, 1999: Andrei N. Lupas, SmithKline Beecham Pharmaceuticals, Collegeville, PA, "Protein Taxonomy"
- October 15, 1999: Menachem Gutman, Laser Laboratory for Fast Reactions in Biology, Tel Aviv University, Israel, "The Trajectory and Dynamics of Ion Propagation Through Large-Pore Ion Channels"
- October 18, 1999: Axel Brunger, Yale University, Dept. of Molecular Biophysics and Biochemistry, New Haven, CT, "Structural Insights into the Mechanism of Synaptic Vesicle Fusion"
- October 25, 1999: Angela Gronenborn, National Institutes of Health, Bethesda, MA, "Advances in NMR Structure Refinements"
- November 8, 1999: Viola Vogel, Department of Bioengineering, University of Washington, Seattle, WA, "Fibril Assembly and Single Molecule Mechanics of a Multidomain Protein"
- November 17, 1999: Sebastian Doniach, Applied Physics and Physics, Stanford University, "Parallel Pathways in Protein Folding: X-Ray Measurements and Computer Simulations"
- November 29, 1999: Paul R. Selvin, Department of Physics and Biophysics Center, University of Illinois, "Conformational Changes in Ion Channels (nerves) and Actomyosin (muscle) Measured by Advanced Fluorescnece Methods"
- December 6, 1999: Vladimir Chernyak, Department of Chemistry, University of Rochester, Rochester, NY, "Collective Excitations in Biological Antenna Complexes and Dendrimeric Supramolecules"
- January 31, 2000: Charles L. Brooks, Scripps Research Institute, La Jolla, CA, "Dielectric Response and Electrostatic Interactions in Protein Stability"
- February 2, 2000: Robijn Bruinsma, "UCLA" Why Biopolymers Teach Novel Condensed-Matter Physics
- February 21, 2000: Todd J. Martinez, Department of Chemistry, University of Illinois, Urbana, IL, "Photoinduced cis-trans isomerization and Ring-opening Reactions: From Gas Phase Photochemistry to Photoactive Proteins"
- March 6, 2000: Peter Kollman, University of California at San Francisco, "Molecular Dynamics on Protein and Nucleic Acid Systems"

- March 13, 2000: Yoshitaka Tanimura, Institute for Molecular Science and the Graduate University for Advanced Studies, Okazaki, Japan, "Reaction Rates and Raman Spectra of Double Well Tunneling Systems in Consensed Phases"
- March 22, 2000: Paolo Carloni, International School for Advanced Studies Condensed Matter Sector, Trieste, Italy, "Molecular Dynamics Studies on the Potassium Channel"
- March 27, 2000: Jeffrey Skolnick, The Danforth Plant Science Center, St. Louis, MO, "Prediction of Protein Structure and Function on a Genomic Scale"
- April 10, 2000: Stanley K. Burt, NCI/FCRDC, Frederick, MD, "Quantum Chemical Investigations on the Catalytic Mechanisms of Thymidine Phosphorylase and DNA Polymerase Beta"
- April 19, 2000: Sergei Sukharev, Department of Biology, University of Maryland, "The Gating Transition of Large Mechanosensitive Channel, MscL"
- April 24, 2000: Irwin Tobias, Rutgers University, Piscataway, NJ, "DNA as a Thermally Fluctuating Elastic Rod"
- May 4, 2000: John Kennis, Dept. of Chemistry, University of California and Physical Biosciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, "A new pathway of excited state energy deactivation in carotenoids: singlet to triplet state conversion on the femtosecond timescale in a photosynthetic antenna"
- May 5, 2000: Michael S. Lee, Department of Chemistry, University of California at Berkeley, Berkeley, CA, "New Polarized Atomic Orbital and Local Correlation Methods in Quantum Chemistry"

The Resource has also organized a praised Biological Physics 001 lecture series[‡] which was held at the UIUC Physics department. The following speakers presented highly attended talks:

[‡]URL: `http://www.ks.uiuc.edu/Services/SpecialLectures/BP001/`

Jan. 21, 2000:	Howard Berg (Harvard U.) "How bacteria swim and navigate"
Jan. 28, 2000:	Klaus Schulten "How muscle pulls"
Feb. 4, 2000:	Enrico Gratton "How oxygen spreads in tissue"
Feb. 11, 2000:	Colin Wraight "How cells conduct protons"
Feb. 18, 2000:	Nancy Makri "How cells conduct electrons"
Feb. 25, 2000:	Paul Selvin "How nerves fire"
Mar. 3, 2000:	Antony Crofts "How cells part protons and electrons"
Mar. 10, 2000:	Klaus Schulten "How nature harvests sunlight"
Mar. 24, 2000:	Martin Gruebele "How proteins fold in vitro"
Mar. 31, 2000:	Zan Luthey-Schulten "How proteins fold in silico"
Apr. 7, 2000:	Andy Belmont "How cells store their genes"
Apr. 14, 2000:	Robert Clegg "How molecules move in cells"
Apr. 21, 2000:	Ian Robinson "How viruses infect"
Apr. 28, 2000:	Joseph Malpeli "How the brain sees"

The Resource participated on March 3 and 4, 2000, in the Beckman Institute's open house in conjunction with the UIUC College of Engineering. The Resource presented a demo 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 3D projection facility has been extensively used for scientific, dissemination and training purposes. The facility is regularly included on UIUC tours by federal and state officials, and is operated by the Resource personnel. Visitors to the facility over the past funding period included: Mehmet Sarikaya, University of Washington; Tom Huang, University of Illinois; Dr. Wang, Georgia Tech; Congressman Ewing, State of Illinois, US Government; Paolo Carloni, Int. School. Adv. Studies., University of Trieste; Diane Yi, Beckman Institute; Rich Furst, VA Linux; Tom Bongiorno, VA Linux ; John Phillips, Indiana University ; Carlos Bustamante, University of Oregon; C. Langer, MIT; Mair E.A.Churchill, University of Colorado, Denver; Janet Dyson, Scripps Research Institute; Andrei N. Lupas, SmithKline Beecham Pharmaceuticals; Ross Giles, Boston University ; Menachem Gutman, Tel Aviv University ; Leslie A. Brothers, Krannert Art Museum ; Steven Chu, Stanford University ; Fangqiang Zhu, University of Illinois; Karen Wells, University of Illinois; Luis Serano, EMBL - Heildelberg ; Angela Groenborn, NIH; Jiri Jonas, Beckman Institute; Larry Smarr, et al., NCSA; Viola Vogel, University of Washington, Seattle ; Raphael Levine, Hebrew University; Sebastian Doniach, Stanford University; Paul Selvin, University of Illinois; Andrew Dalke; Vladimir Chernyak, University of Rochester; David Crockett, Sun Microsystems; Howard Berg, Harvard University; Luis Bagatolli, University of Illinois; Charles L. Brooks III, Scripps Research Ins.; Dr. Zu, Stanford University; Jonathan Fridman, University of Illinois; Peter Kollman, University of California, San Francisco ; Tom Moore, Photosynthesis Center, Arizona State Univer-

sity ; Lisa Ankenbrand, N/A; Stanley Burt, Advanced Biomedical Computing Center, Frederick, MD; Susan Rapp, University of Illinois; Martin Greven, University of Illinois; Irwin Tobias, Rutgers University; Sergei Sukharev, University of Maryland; participants of MD meeting.

VMD demos in the NCSA Cave were given by Uv Ramesh-Chandra, NCSA; Peter W. Kim, NCSA; Volodymyr Kindratenko, NCSA; David P. Bock, NCSA

Additionally, 12 VMD demos were given to groups of prospective graduate students.

Our web server is regularly maintained to give Internet users access to publications, images, and routine activities of the Resource. A new powerful search engine software (ht://Dig) makes the Resource site even a more effective tool than before.

The Resource's future plans in this area include:

- MD Forum for MD benchmarking discussions and MD Salon for research discourse will be established and added to the already existing suite of tools offered by the Resource.
- An MD analysis database will be started to include the Resource's as well as 3rd parties' tools.
- MDTools will be developed further this year to include a new tracking program and a new trajectory file format converter.
- Slide tours will be developed for the three software projects and will exhibit the functionality traditionally associated with tutorials and searchable manuals.

Training

As in previous years the training activities at the Resource overlap with the service and dissemination efforts. In addition to the information provided in the previous Service section and in the following Dissemination section, the Resource's Principal Investigators advise graduate students in their respective departments and offer rotation opportunities to undergraduates. The Resource organized several events which are reported in the Service and Dissemination sections (meetings, seminars, open house, and more). The design of on-line tutorials and slide tours is in progress and will be another dominant means of technology transfer. This will increase the dissemination of the Resource's software and methods and the number of users benefiting from them. A recently submitted proposal to the Burroughs Wellcome Foundation is intended to establish a springboard for an active training program that will interface Biology and Physics through the use of BioCoRE and other software technologies and methods developed at the Resource.

The Resource's projection facility was used for Physics, Biophysics and Chemistry classes. Long and short-term visitors to the Resource benefited from on-the-job training and hands-on experience with the software developed and computational expertise residing at the Resource. These included:

- Professor Robijn Bruinsma, UCLA (Winter 2000)
- Felix Autenrieth, University Stuttgart, Germany (Summer and Fall 99)
- Dr. Emadeddin Tajkhorshid, German Cancer Research Center, Heidelberg University (Summer 99)
- David Craig, U of Washington (Summer 99)
- Professor Attila Gursoy, Bilkent University, Ankara, Turkey (Summer 99)

The direct and intensive interactions with the software developers and the application scientists, already well versed with the software tools, made the visitor's stay at the Resource particularly advantageous.

The Resource maintains a small, yet well-stocked, textbook library. We presently subscribe to 17 journals including: Science; Nature; C++ Journal; Sys Admin Journal; Nature Structural Biology, Chronicle of Higher Education; Linux Journal; Dr. Dobb's Journal; Mac World; Structure with Folding and Design; Physics Today; Trends in Biochemical Sciences; Biophysical Journal; Journal of NIH Research.

The Resource expects to continue to purchase books, to keep our journal subscriptions, and possibly add new ones, depending on our research needs and availability of funds. The Resource library is well cataloged. The catalog is available to Resource members on the web[§] and the library has become an important training tool for members and visitors.

Many of the research and development activities at the Resource are performed by graduate students. The graduate assistants typically leave the Resource once they complete their education. The list below includes M.A. and Ph.D. recipients, postdoctoral associates and undergraduates who received their training at the Resource during the past year.

Ph.D. Students

1. Hui Lu, Nuclear Engineering, October 1999, "Molecular Dynamics Simulation of Force-Induced Protein Domain Unfolding". Moved to Danforth Plant Science Center, St. Louis, MO.

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

2. Robert Brunner, Electrical and Computer Engineering, May 2000, "Versatile Automatic Load Balancing with Migratable Objects". Assumed a programming position with the Resource.

Postdoctoral Associates

1. Jerome Baudry, Staff Member, TransTech Pharma, N.C.
2. Dorina Kosztin, Scientific Software Consultant, UIUC School of Chemical Sciences
3. Christian Forst, Technical Staff Member, Biosciences Division, LANL
4. Margit Moelhoff

Past and Current Undergraduate Trainees

- Paul Grayson: REU, Physics, Summer 1999 (MIT)
- Joanna Francis: Sysadmin Assistant, 1999- (UIUC)
- Amit Mehta: University of Illinois, Physics REU, Summer 1999 (Cornell)
- David Norris: VMD Assistant, 1999- (UIUC)
- Matt Wolak: NAMD Assistant, 1999- (UIUC)
- Joseph Brumleve: Media and Web Assistant, 2000- (UIUC)
- Justin Wozniak: 1998- (UIUC)

Three new graduate students will join the Resource this summer and two REU students are expected to spend the summer at the Resource.

Dissemination

The Resource continues to fully utilize the wide array of communication and dissemination tools available today. The Resource's web site[¶] represents the group's scientific efforts to the outside world. The site offers scientific, technical and administrative information, including ongoing research projects, main research accomplishments, image and movie galleries, software distributions, a publication list with abstracts and full-text files when permitted by publishers, information about the people in the Resource, as well as the

[¶]URL: `http://www.ks.uiuc.edu/`

Resource's seminar series, special events organized by the Resource, job announcements, training and learning opportunities, and more. A web search indicates that the Resource's visibility has increased tremendously and there are close to 1200 links to the Resource's site from other sites, an increase of almost 100% compared to the 600 links located in the year before.

A major overhaul of the Resource's web site is near completion 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 a web-based database, 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). This type of data is an important resource in guiding the development and maintenance of the site, and serves to identify general trends outside the Resource. Latest statistics are presented in a descending order, as determined by the estimated monthly average accesses:

- Entire TB Site (http://www.ks.uiuc.edu/) ∼ 72,000 / month
- VMD ∼ 43,000 / month
- NAMD ∼ 11,500 / month
- Research ∼ 9,500 / month
- Papers ∼ 6,000 / month
- BioCoRE ∼ 3,250 / month
- Galleries ∼ 1,800 / month
- Seminars ∼ 1,500 / month

An access is defined as a request for an HTML page on a given server excluding images. More reliable measures of visits received on the site will be implemented as they become available.

All software manuals and documentation are posted on the Resource's web site, as well as images and results of recent work; research and development accomplishments are published in professional journals and are posted on the web; lectures and talks on the Resource activities are given all over the world; various documents, such as reports and brochures, are periodically produced and mailed to colleagues, prospective members, and

federal offices, as well as posted on the web[‖]. Videotapes, slides and CDs are created in response to requests from funding agencies, collaborative groups, local administrators and users. A video on Interactive Molecular Dynamics and the use of a Haptic Device has recently been produced and is enclosed with this report (Appendix E). Over 100 copies of Resource videotapes have been distributed around the world in the past 12 months. The Resource staff and members continuously report key findings and systematically disseminate new knowledge produced by the Resource. Announcements for VMD and other Resource software were sent to leading magazines and papers such as Acta Crystallographica, Science, Chronicle of Higher Education, Reviews In Computational Chemistry, Journal of Applied Crystallography, and the Journal of Computational Chemistry. The announcements appeared in Science (Feb. 4, 2000 issue), Access Magazine (NCSA, March 2000), and are being considered by the others. A story on VMD appeared in the May 1999 issue of Computer Graphics World as part of the Tech Watch column[**]. Images produced by Resource members using VMD and NAMD appeared in IEEE Potentials (April/May, 2000 issue) and are set to appear in :

1) Textbook expected to be published in July 2000. "BSCS Biology: A Molecular Approach"(Blue Version, 8th edition) published by Everyday learning Corporation.

2) Textbook by David E. Metzler: "Biochemistry: The Chemical Reactions of Living Cells – A Text and Reference Book" 2nd Edition. Academic Press, 2000.

Resource graphics are regularly used in posters and talks by non-Resource members. Press releases on research findings initiated by the Resource have been posted on various e-boards and in papers and magazines including recent releases on papers in Nature [79] and in Biophysical Journal [54].

Columbia Pictures requested and received our permission to use our figures in the motion picture "THE HOLLOW MAN" directed by Paul Verhoeven, with special effects by Sony Pictures Imageworks.

The Resource's web site is the principal means of distribution for our software and information on prototype modeling projects and related activities. The Resource's key software projects NAMD, VMD and BioCoRE are freely available on the web[††] and employ pages that are designed in a related fashion. VMD and NAMD are accompanied by searchable documents: a User's Guide for general users, and a Programmer's Guide for those who want to modify the programs. The new VMD, NAMD and BioCoRE licenses

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

[**]URL: `http://www.cgw.com/`

[††]URL: `http://www.ks.uiuc.edu/`

and registration procedures are essentially similar and have made the entry process very user-friendly. All user information is now stored in a database and, as a result, more reliable data is obtained and the monitoring of software usage and the knowledge of the users' profile and preferences is much more extensive and reliable. To determine the number of NIH-funded users and assist the agency in its efforts to assess the benefits to NIH sponsored research, users are required to indicate if their work is NIH-funded as part of the registration process.

VMD for Windows (VMD 1.4) was released 1/2000. As of 5/1/2000 there have been over 3000 registered VMD 1.4 users, of whom 400 are NIH-funded. There have been 491 source code downloads, and 3029 binary downloads. 56% of the binary downloads were for the Windows 95/98/NT version, and 44% of the binary downloads were for one of the Unix versions (AIX, HP-UX, IRIX, Linux, Solaris, Tru64). The Windows version of VMD is a definite hit! There have been over 43,000 accesses per month to the VMD section of the website in past year. 129 VMD demos were given at the Resource and at NCSA in the last 12 months.

NAMD 2.1 was released in November, 1999. A current estimate of the number of NAMD 2.1 users is 543, with 81 NIH-funded users (15%).The total number of NAMD 2.1 downloads since the release is 881 with 572 binary (∼65%) and 309 source (∼35%) downloads. Over 40% of the downloads were for the Linux OS. In the past year there have been 11,500 accesses per month to the NAMD section of the website.

Across both programs, roughly 15% of all users are funded by NIH and we expect that this percentage will increase as the software become even more easy-to-use and available on more affordable platforms. We provide user support through e-mail and the average response time, desired and actual, is within 48 hours.

Online newsgroups have been a major channel for the dissemination of VMD, NAMD, and BioCoRE. Newsgroups used for dissemination include:

BioCoRE bionet.announce
bionet.biology.computational
bionet.molbio.proteins
bionet.molec-model
bionet.software
bionet.software.x-plor
sci.chem
VMD mailing list
Computational Chemistry mailing list

NAMD bionet.announce

bionet.biology.computational
bionet.molec-model
bionet.software
bionet.software.x-plor
Computational Chemistry List
Beowulf Announcement List

VMD VMD mailing list
bionet.announce
bionet.biology.computational
bionet.molec-model
bionet.software
bionet.software.x-plor
comp.os.linux.announce
comp.sys.sgi.announce
comp.sys.sgi.graphics
sci.chem
Computational Chemistry List chemistry@ccl.osc.edu
OpenGL web site products@opengl.org
http://www.freshmeat.net/
Many WWW software databases

VMD and NAMD brochures were totally redesigned in the past year and a BioCoRE brochure has been developed (see Appendix D) . The brochures have been used to announce the new VMD and NAMD versions and the first release of BioCoRE. They have been mailed to over 500 research groups, institutions and individuals around the world. They are being distributed at events attended by the Resource members.

The new BioCoRE page has been established at: http://www.ks.uiuc.edu/Research/biocore/.
The newly updated research section is at http://www.ks.uiuc.edu/Research/
The images and movies representing the Resource's efforts are at
http://www.ks.uiuc.edu/Overview/gallery/ and
http://www.ks.uiuc.edu/Overview/movie_gallery/, respectively.

Finally, during the past year, the Resource has published and/or submitted 33 scientific papers (see pp. 67-70) The Resource also makes its publications available as preprints and reprints in the form of Technical Reports and PDF files. The manuscripts are maintained in a web-based database accessible to Internet users and are made available upon request[‡‡].

[‡‡]URL: `http://www.ks.uiuc.edu/Publications/Papers/`

The PI has presented the following lectures during the past year:

- August 5, 1999: WATOC'99 Conference, "Quantum Mechanical Description of the Picosecond Photoprocess Initiating Proton Pumping in the Protein Bacteriohodopsin."
- October 8, 1999: Wesleyan University Seminar, "How Nature Harvests Sunlight."
- November 15, 1999: Science Applications International Corporation (SAIC), San Diego, CA, "Interactions and mechanisms controlling assembly and function at multiprotein systems in membranes."
- November 18, 1999: Beckman Institute External Advisory Committee lecture, "Atomic force microscopy "in vivo", "in vitro", and "in silico."
- November 19-28, 1999: International Conference on "Chemical Reaction Dynamics in Many Body Chemical Systems," Kyoto, Japan, "Structure, dynamics and function of the purple membrane of Halobacterium salinarium."
- January 13-15, 2000: La Jolla, CA, Quantitative Challenges in the Post-Genomic Sequence Era, a Workshop and Symposium, "Interactions and mechanisms controlling assembly and function of multiprotein systems in membranes."
- February 24-March 1, 2000: Durango, CO, Keystone Symposia, Macromolecular Assemblies at Work: Application of Physics, Chemistry, and Mathematics to Biology, "Interactions and mechanisms controlling assembly and function of multiprotein systems in membranes."
- March 8-10, 2000: Arlington, VA, NSF Workshop on Dynamic Data-Driven Application Systems, "Steered computing - A powerful new tool for molecular biology."
- March 28, 2000: Juelich Research Center, Germany, "Steered computing - a powerful new tool for molecular biology."
- March 25-30, 2000: Regensburg, Germany, "Symposium Biology and Physics, "Function, Architecture and Mechanism of Light Harvesting Systems in Photosynthetic Bacteria."
- April 5-8, 2000: University of York, York, UK, Modeling Biomolecular Mechanism Symposium, "Steered molecular dynamics to study biopolymer association and stretching."
- April 16-17, 2000: University of Illinois, Beckman Institute, Urbana-Champaign, IL, Parallel MD Development and Use — Challenges and Opportunities Workshop, "Steered Molecular Dynamics - a Powerful Tool for Molecular Biology."

- April 21-May 4, 2000: University of Western Australia, Nedlands, W. Australia, Master Classes in Molecular Biophysics —

Lecture 1: "The photosynthetic unit of purple bacteria: From light absorption to ATP synthesis,"

Lecture 2: "Modelling and verifying protein structure and function - a case study from photosynthesis,"

Lecture 3: "Navigating through proteins: hands-on graphics,"

Lecture 4: "Molecular dynamics simulations of the mechanosensitive ion channel."

Lecture 5: "How to do molecular dynamics simulations, exemplified for the mechanosensitive channel,"

Lecture 6: "Exploring ion channels and other membrane proteins through molecular graphics,"

Lecture 7: "Atomic force microscopy in vivo, in vitro, and in silico,"

Lecture 8: "Analysis of molecular dynamics simulations,"

Lecture 9: "Animation of molecular dynamics simulations,"

Lecture 10: "Diffusion effects in MRI and MRI Microscopy,"

Lecture 11: "Stochastic quantum systems rule biomedicine."

- May 10, 2000: University of California, San Diego, Computational Sciences seminar series keynote speaker, "Steered computing - a powerful new tool for molecular biology."

During the past year the PI served on the following committees:

- Appointments and Promotions Committee, Physics Department, UIUC
- Ph.D. Qualifying Exam (August 30-31, 1999), Physics Department, UIUC
- Biophysics Search Committee, UIUC
- Biotechnology Faculty Advisory Committee member, UIUC
- Biotechnology Council Member, UIUC
- Post Genomics Committee, UIUC
- Bioengineering Study Committee, UIUC.

During the past year the PI was a reviewer for

- Swiss National Science Foundation
- Journal of Molecular Modelling
- Institute of Physics
- Physical Review and Physical Review Letters
- Israel Science Foundation
- Journal of Medicinal Chemistry
- Journal of Physical Chemistry
- Biophysical Journal
- Journal of Chemical Physics
- National Institute of Health
- National Science Foundation
- Nature
- Science
- Proceedings of the National Academy of Sciences
- Proteins, Structure, Function, and Genetics
- Journal of Computational Physics
- Europhysics Letters
- Journal of Computational Chemistry
- Journal of Molecular Biology
- Nucleic Acids Research

During the past year research personnel of the Resource have participated and/or presented contributions at the following meetings and institutions:

May 1999

- HIPS 2000, 5th Intl. Workshop on High-Level Parallel Programming Models and Supportive Environments, Cancun (Mexico), "How to overcome obstacles to the acceptance of novel high-level parallel programming approaches" (Laxmikant Kale)

- 5th SIAM Conference on Applications of Dynamical Systems, Snowbird, Utah, "Stability Analysis of area Preserving Maps" (Robert Skeel)

June 1999

- Summer School in Termoli, Italy "Mathematics of Cell Physiology and Proliferation," "Understanding Light-Harvesting Systems: A Complex Interplay Between Symmetries and Atomic Details," (Thorsten Ritz)

July 1999

- Ab Initio Quantum Dynamics: Applications to Photochemistry, Radicals in the Rockies Workshop, Telluride, CO (Todd Martinez)

August 1999

- Volumetric Properties of Biological Objects, Toronto, Canada (Dorina Kosztin)
- Computation of Biochemical Pathways and Genetic Networks, Heidelberg, Germany, "Phylogenetic Analysis of Metabolic Networks." (Christian Forst)
- 218th National ACS meeting, New Orleans, LA, "Retinal isomerization in Bacteriorhodopsin," (Jerome Baudry)
- VI International Symposium on Magnetic Field and Spin Effects in Chemistry and Related Phenomena, "A model for vision based magnetoreception in birds," (Thorsten Ritz)
- First-Principles Studies of Photoinduced Isomerization and Electron Transfer, Electronically Nonadiabatic Processes in Gaseous, Cluster, and Condensed Media, ACS Symposium, New Orleans, LA (Todd Martinez)

September 1999

- Visit and presentation to the group of R. Van Grondelle, Amsterdam, The Netherlands, "Light-Harvesting by Carotenoids: BI State Symmetry and its role in excitation energy transfer." (Ana Damjanovic)
- XIII International Biophysics Congress, New Delhi, India, "Light-Harvesting by Carotenoids in Photosynthesis," (Ana Damjanovic)

October 1999

- Workshop on Interactions Between Chlorophylls and Carotenoids in Photosynthesis, Antalya, Turkey, "Semiempirical Theory of Carotenoid-Chlorophyll Excitation Transfer/Application to Light-Harvesting systems of Purple Bacteria and Dinoflagellates," (Ana Damjanovic)
- Visit and Presentation to Paolo Carloni's group, Trieste, Italy "Excitation Energy Transfer in Light-Harvesting Complexes," (Ana Damjanovic)
- Photochemistry from First Principles, Hope College (Todd Martinez)
- Photochemistry from First Principles, Calvin College (Todd Martinez)

November 1999

- CMB/MS Research Symposium, Urbana, IL, "Using Kirchhoff Equations to Study the Conformation of short DNA Loops," (Alexander Balaeff)
- Supercomputing 99, BioCoRE Demonstration, Portland, OR, "Distributed Interactive Molecular Dynamics within BioCoRE," (Kirby Vandivort and Justin Gullingsrud)
- Collaboratory for Research on Electronic Work, University of Michigan, Ann Arbor, MI (David Brandon)

December 1999

- Molecular Dynamics with Nuclear and Electronic Quantum Effects, Center for Simulation of Advanced Rockets, University of Illinois at Urbana-Champaign (Todd Martinez)
- Ab Initio Quantum Photodynamics, Michigan State University, (Todd Martinez)

February 2000

- Biophysical Society 44th Annual meeting, New Orleans, LA (Rosemary Braun)
- Biophysical Society 44th Annual meeting, New Orleans, LA (Alexander Balaeff)
- Biophysical Society 44th Annual meeting, New Orleans, LA (Barry Isralewitz)
- Biophysical Society 44th Annual meeting, New Orleans, LA, (Justin Gullingsrud)
- Photoinduced cis-trans Isomerization and Ring-Opening Reactions: From Gas Phase Photochemistry to Photoactive Proteins, Theoretical Biophysics Group, Beckman Institute, University of Illinois at Urbana-Champaign (Todd Martinez)

March 2000

- American Physical Society meeting, Minneapolis, MN, "Using the theory of elasticity to model the structure of DNA loops," (Alexander Balaeff)
- American Physical Society meeting, Minneapolis, MN, "Pair Excitations, Collective Modes and Gauge Invariance in the BCS - BEC scenario," (Ioan Kosztin)
- First-Principles Quantum Molecular Dynamics, Potential Energy Surfaces: From Polyatomics to Macromolecules, ACS Symposium, San Francisco, CA (Todd Martinez)

April 2000

- Multiscale Computation in Chemistry and Biology, Eilat, Israel, "Multiple Time Scale Methods for MD," (Robert Skeel)
- Molecular and Electronic Nanostructures Seminar Series Nanohour, University of Illinois, Urbana-Champaign, IL, "Molecular Dynamics Studies of the Gating Mechanism of a Mechanosensitive Ion Channel," (Justin Gullingsrud)
- ITG Forum, Beckman Institute, UIUC, "BioCoRE: A Collaboratory for Structural Biology," (Kirby Vandivort)
- UMR Association for Computing Machinery, University of Missouri - Rolla, "VMD - High Performance Molecular Visualization," (John Stone)
- Computer Science Department, Notre Dame University, "VMD - High Performance Molecular Visualization," (John Stone)

May 2000

- The Fifth International Conference on Human Interaction with Complex Systems, University of Illinois, Urbana-Champaign, IL, "BioCoRE and Interactive Molecular Dynamics" poster presentation (Kirby Vandivort, Robert Brunner)

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