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Contents

The NIH Resource for Macromolecular Modeling and Bioinformatics makes computational technologies available to biomedical researchers studying the molecular apparatus in biological cells. The rapid advances in the biomedical sciences that provide sequences and structures of the proteins that constitute the molecular machinery of cells with increasing detail can be sustained only with the help of modern information technologies. Fortunately, these technologies are themselves evolving at a revolutionary pace, rendering tools that are becoming more powerful and cheaper every day. However, to harness the power of modern computing requires ever increasing efforts and human ingenuity. Fortunately, the NIH National Center for Research Resources through support of its Computational Resources makes the necessary investments that ensure the availability of advanced computing technologies for biomedical researchers. During the past year our Resource has again made excellent use of this support through development of widely distributed software as well as through pioneering science projects.

In particular, three dramatic technology developments have been identified and exploited by the Resource for Macromolecular Modeling and Bioinformatics, the development of powerful graphics chips in the computer game industry, the development of commodity computer clusters and terascale computing platforms, as well as the continued proliferation of web-based tools in company-wide computing. Below we outline how these developments have been incorporated into new software furnished by our Resource.

Graphics chips. Until recently, the needs of biomedical scientists for the high-end graphics required to render complex biomolecular structures could only be met by workstations in a price range of several ten-thousand dollars. Driven by the computer game industry, these needs can be met today by personal computers that are endowed with graphics boards costing a few hundred dollars. The latest board, based on the NVidia Geforce 3 graphics chip and priced at $400, permits the rendering of 160,000 atom structures at 8 frames per second, a feat that was unimaginable a few years ago even for highly priced graphics computers. To utilize this opportunity requires, however, the same effort that the game industry invests in development of its software. The Resource for Macromolecular Modeling and Bioinformatics through its program VMD has succeeded in providing biomedical researchers a tool that permits use of the latest graphics chips on essentially all platforms, e.g., Linux workstations, PCs and Apple computers. Over ten thousand users have downloaded the software so far. In its most recent version the software integrates structural and sequence information, providing an essential tool for the postgenomics era of the life sciences.

Workstation clusters and terascale computers. Another dramatic development in commodity computing essential for life science research occurred through the speed-up of

processors for PCs, network switches and the Linux operating system. One can purchase today for a price of less than $30,000 a networked (100 Mbit/s) cluster of workstations that operate about as fast as a 128 processor Cray T3E on a molecular modeling program, optimized for both machines. To harness the power of cluster computing at a price reduced by a factor of about 10 (relative to the Cray T3E) has become possible through the long term investment in parallel molecular dynamics at the Resource for Macromolecular Modeling and Bioinformatics. Our Resource was one of the first groups in computational science that adopted, to the greatest benefit of biomedical research, cluster computing in 1992 using NCRR funds. Designing its software from the ground up for parallel computing paid off and places the Resource program NAMD and life science researchers at a unique advantage today. No other modeling program meets the performance of NAMD on commodity clusters executing the most demanding simulations at an extremely low price tag. Through cooperation with the Scyld group of Linux providers the operation of clusters and execution of NAMD can be realized by non-experts; the rapid increase of the use of NAMD with about thousand recent downloads underscores the great return on NCRR's investment.

This investment will bear even more dramatic fruits in the framework of terascale computing. The National Science foundation has funded a computer that operates at teraflop speeds and will become available to US scientists at the Pittsburgh Supercomputer Center this summer. Funding for a similar installation at the NSF Supercomputer Center in Illinois (NCSA) is expected later this year. However, teraflop speed can be achieved only through use of thousands of processors in a single computation and utilization of the new resources requires modeling programs that run effectively for such systems. The program NAMD has shown already to run effectively on a preliminary version of the Pittsburgh terascale machine with 256 processors (TCS1) that can execute a 1ns simulation of a 90,000 atom biomolecular system within less than two days for the most demanding simulation conditions (full electrostatics, constant pressure). No other modeling program can meet this challenge. The program NAMD provides hence the unique access to terascale computing for biomedical researchers.

Web-based enterprise computing. Leading corporations have embraced the use of the web through so-called enterprise computing software with great benefit to their operation. The software provides data accessible to relevant employees, permits world-wide communication and data processing, and provides software tools specific for a corporation's business. The software is web-based using the Java programming language and conforming to html and XML standards. As a result, the tools and data of enterprise computing are available through browsers and, therefore, through all computing platforms and at any location. Life science, like corporations, forms in many of its subfields intricate networks of research communities that can tremendously benefit from the same

tools, e.g., improving communication and reducing costs through higher productivity. But like for corporations the tools come at the price of development costs. Through the collaboratory software initiative of NCRR the Resource for Macromolecular Modeling and Bioinformatics has ceased the opportunity to develop the needed tools in the form of the Resource's new program BioCoRE. The Resource for Macromolecular Modeling and Bioinformatics has utilized the new funds, that amount to about half of the previous funds of the Resource, solely for an intense software development effort seeking to provide a comprehensive communication and web-computing environment for life science. BioCoRE furnishes already after less than two years of development an impressive list of utilities and is now beginning to be deployed by Resource scientists, Resource collaborators and independent groups. The utilities that BioCoRE provides include browser-based tools for molecular graphics as well as for job submission and monitoring, for joint molecular graphics sessions at different sites, for training in molecular modeling, and for a comprehensive communication environment in which collaborating life scientists can share many kinds of scientific data with few key strokes. It is already obvious that BioCoRE will become an indispensable tools for life science researchers.

Science projects. The software of the Resource for Macromolecular Modeling and Bioinformatics described above emerges from science projects carried out in collaboration with mainly experimental research groups. These projects are by and large extremely demanding, involving mechanical manipulations of biomolecular systems that are studied by single molecule experiments, predictions of complex structures, e.g., protein - DNA complexes, or very large systems, e.g., protein membrane complexes. The Resource for Macromolecular Modeling and Bioinformatics has pioneered, in particular, two types of modeling studies, so-called force spectroscopy and simulations of protein function in integral membrane environments.

Force spectroscopy seeks to understand mechanical functions of proteins. Through its steered molecular dynamics methods the Resource has become the leader in the field of protein mechanics. During the past year, the Resource has published two reviews of this field and together with its collaborators has initiated new studies of the extracellular matrix protein fibronectin and the muscle protein titin, focusing new simulations on large scale stretching of these proteins that leads to complete unfolding. The new simulations require embedding of the systems in a water bath large enough to permit complete unfolding and incorporating therefore over 120,000 atoms. The Resource has also taken first steps towards a revolutionary simulation method, interactive molecular dynamics, in which proteins are manipulated in a running simulation through a graphical interface combining the NAMD and VMD programs. In using this method a so-called haptic device permits users to manipulate systems in six degrees of freedom and to feel the compliance of the molecules through force feed-back.

The Resource had been involved for over a decade in simulations of membrane proteins. Its studies of lipid bilayers and of the membrane proteins photosynthetic reaction center and bacteriorhodopsin as well as of photolipase A2, that adheres to membranes, were the first of its kind. Until recently, few membrane proteins were structurally resolved, but this situation has changed dramatically with about twenty different membrane proteins solved. This has brought about a great opportunity for fundamental investigations in cell biology, but modeling studies complementing the experimental efforts are extremely demanding: embedding proteins into properly hydrated lipid bilayers leads to large simulated volumes with about 100,000 atoms. Simulations must account for the Coulomb interactions faithfully and need to be carried out under constant pressure conditions. The necessary simulations are the primary domain of the Resource program NAMD and the Resource with its collaborators could address a record number of research problems using this tool. Projects during the past year included investigations of the purple membrane of halobacteria, the light harvesting complex LH2 of purple bacteria, the potassium channel KscA, the mechanosensitive channel MscL, as well as two proteins of the aquaporin family, AQP1 and GlpF, and have lead already to published as well as submitted papers. Since NAMD is available to all researchers and will soon be compatible with two of the most popular simulation programs and force fields (AMBER and CHARMM), the opportunity of studying membrane proteins will be available to all biomedical scientists.

Training, Service, Dissemination. The Resource for Macromolecular Modeling and Bioinformatics places great emphasis on training, service, dissemination. Through its clear focus on software distribution, it is in a unique position to do so effectively, for example through the popular Resource web site (`http://www.ks.uiuc.edu`) that receives about 250,000 hits per month and serves typically 15000 Megabytes of information during this time period. The Resource effort is described in great detail further below, demonstrating the strict emphasis that the Resource places on its outreach.

Gating in the mechanosensitive channel MscL

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 [1] as well as mammals [2, 3]. 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 [4]. Several studies [5–7] have confirmed the importance of this channel for osmoregulation of the bacterial cell*.

Results of the simulations of the protein in the full membrane-water system reflect a protein that is quite stable in the closed state. This is to be expected from patch-clamp data [8], which reveal a channel with zero conductance until significant tension is applied. Large-scale changes in the shape of the protein could not be expected during the progress of a 3 ns simulation; it is, therefore, possible that a much longer simulation could reveal a somewhat different closed state. We believe that we have described the essential features of this protein on the time scale of several nanoseconds, and find encouraging correspondence with experiments. Fluctuations on the scale of individual residues were found to be in good agreement with corresponding measurements from ESR experiments, confirming the validity of our protein model. Water penetration in the pore was found to extend only to hydrophilic residues, i.e., only as far as Thr25. This result lends support to proposed mechanisms of MscL gating that postulate a change in the solvent environment of hydrophobic residues in the pinched region of the protein during gating.

Though a realistic simulation of MscL must include the membrane and surrounding water, we can investigate the mechanics of the protein itself without these external media. To this end we conducted a series of simulations of the same protein structure as in the membrane simulations, but with no membrane or water present. The simulations were conducted at constant surface tension and zero normal pressure. To our knowledge, this is the first time surface tension has been used in molecular dynamics simulations to elicit a conformational change in a protein.

Our simulations of the bare protein using an applied surface tension to induce conformational change provided remarkably consistent results: the protein retained its secondary structure while radically reforming its tertiary structure to form a large pore. Retention of secondary structure was an important validity check since the native lipid environment would not have allowed alternative hydrogen bonds to form. The observation that the transmembrane helices flattened out corresponds well with recent measurements made of the effect of membrane thickness on MscL gating [9]. In these measurements, it was found that when MscL was placed in a thinner membrane, it remained for a longer period of

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

time in its open state. This would seem to suggest that the open conformation of MscL is flatter than the closed structure.

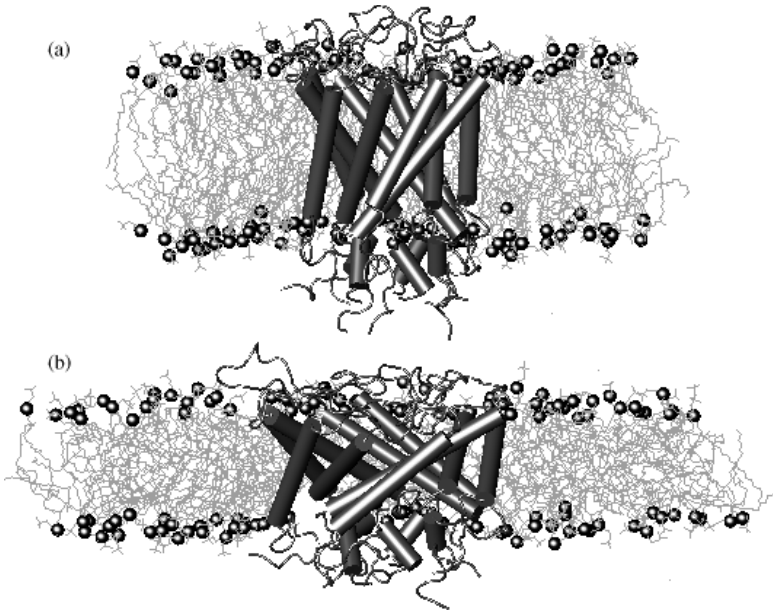

Figure 1: MscL protein in POPC bilayer (a) at beginning of simulation and (b) after 2 ns of applied surface tension.

We have continued our study of the effect of surface tension on MscL by simulating the entire protein-membrane complex. For this simulation we used a model of MscL provided by R. Guy (NIH) in which the first 10 residues of the protein were modeled. Recent studies [10] have suggested that these residues, which unfortunately are absent from the crystal structure, play a crucial role in gating. In the proposed model, the 10 N-terminal residues form a bundle of helices which occludes the pore until conformational changes in the transmembrane segments of the protein pull the bundle apart. We sought to elucidate this role by simulating the gating of the modeled protein through applied surface tension, and also used the steered molecular dynamics technique to pull the bundle apart directly. Our results are in accord with the model of Sukharev et al. [10], in that application of surface tension to the protein-membrane complex caused the transmembrane segments of the protein to exert tension on the N-terminal helix bundle. However, this tension was not sufficient to pry apart the helix bundle. Moreover, the transmembrane segments did not open as widely as proposed in the model.

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The Role of Intersection Topography in Bond Selectivity of *cis-trans* Photoisomerization

cis-trans photoisomerization represents one of the simplest means to convert light into mechanical motion at the atomic scale, and it is widely used in photoactive proteins. Retinal protonated Schiff base (RPSB) is the best known biological chromophore, with five double bonds capable of undergoing photoisomerization. A long-standing question has been the mechanism that selects the bond which isomerizes, particularly the role of the protein environment in "steering" reactivity. Availability of the structures of rhodopsin [11] and bacteriorhodopsin [12–14] coupled with characterization of RPSB solution-phase photochemistry [15–20] provides a unique opportunity to identify this mechanism. Our work has revealed a novel mechanism for this selectivity with significant implications for understanding protein "steering" and the mechanism of vision. Investigations of the photochemistry of RPSB have established that the protein is not an idle spectator - quantum yield (>50% in proteins and ∼20% in solution), selectivity (in proteins isomerization occurs exclusively around a particular bond, whereas in solution there are several photoproducts with 11-*cis* being the most dominant), and time scales (less than 2ps in proteins and 10 ps in solution) are all significantly different in solution and protein environments. Understanding the solution photochemistry is critical since it provides the standard against which one can quantify the "steering" role of the protein environment. We have used accurate *ab initio* quantum chemistry methods, which are necessary for a suitable description of electronic excited states in molecules. The calculations were done *in vacuo* using a realistic analog slightly shorter than RPSB itself, but containing all the double bonds that can isomerize in RPSB. The β-ionone ring is neglected because it is unlikely to have a significant effect on the electronic structure of the conjugated backbone. The calculations concentrated on the two most important possibilities for photoinduced isomerization: torsion around the C_{11}=C_{12} and C_{13}=C_{14} bonds. We have found local minima on the first excited state (S1) associated with isomerization around C_{11}=C_{12} and C_{13}=C_{14}, which are isoenergetic. In both cases, the local minima are found to lie in close geometric and energetic proximity to the corresponding minimal energy conical intersection (CI) - geometries where two electronic states are truly degenerate, providing doorways from excited to ground electronic states. The degeneracy of the two intersections and associated local minima implies that in the absence of an intervening barrier, the two isomerization pathways are equally probable and so should be the two photoproducts: 11-*cis* and 13-*cis*. However, this is not the case in either protein or solution environments. Especially relevant in the present context are the solution results, where a clear preference for the 11-*cis* photoproduct is observed [15–17]. One possible explanation is the existence of barriers (of quite different heights) between the Franck-Condon geometry and the minimal energy CIs. The calculation of the minimum energy

isomerization pathway for the two relevant bonds, however, did not detect any significant barriers to isomerization.

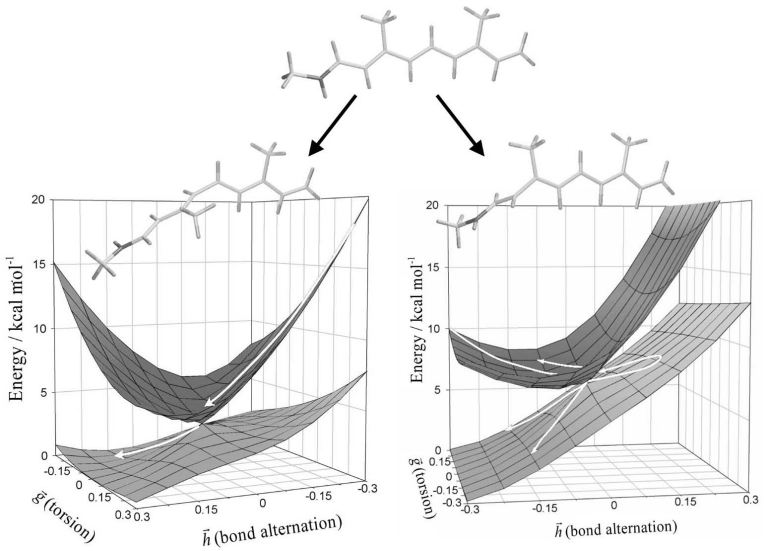

Figure 2: The ground and first excited electronic states of the RPSB analog as a function of displacement along the two coordinates that are most effective in promoting internal conversion from S1 to S0. All other coordinates are fixed at their values at the C_{11}=C_{12} (left panel) or C_{13}=C_{14} (right panel) CI. The C_{13}=C_{14} conical intersection has a "sloped" topography while the C_{11}=C_{12} CI is strongly "peaked." The three graphical renderings depict the structure of the analog at the planar-relaxed geometry, C_{11}=C_{12} conical intersection and C_{13}=C_{14} CI (middle, left and right respectively). The arrows drawn on the computed surfaces provide a qualitative representation of the expected wave packet dynamics.

Thus, we have also characterized the topography of the ground and excited state potential energy surfaces (PESs) in the vicinity of the two minimal energy CIs as a function of the two coordinates that are most effective in promoting efficient internal conversion from S1 to S0. These two coordinates are given by the nonadiabatic coupling vector and the difference gradient vector, denoted as $\vec{g}$ and $\vec{h}$ in Fig. 2 [21]. For RPSB, these are well-described by the bond alternation and relevant C=C torsional coordinates. The resulting 2D PESs are shown in Fig. 2 for both C_{11}=C_{12} and C_{13}=C_{14} minimal energy CIs. The local topographies of the two CIs are quite different, the C_{11}=C_{12} CI is "peaked" and the C_{13}=C_{14} CI is "sloped." [22] These two different topographies are expected to result in quite different dynamics [22, 23]. On the upper PES (S1), the peaked CI is more effective than the sloped one in directing, i.e. "funneling", population to the point of intersection. On the lower (S0) PES, the peaked CI is more effective than the sloped one in directing population away from the intersection, thereby reducing the probability of S0→S1 "up-funneling" [24]. The arrows sketched on the two surfaces demonstrate the expected dynamics for a typical wave packet approaching the CI from the Franck-Condon region. In the case of a peaked CI, the excited state trajectory is clearly directed toward

the intersection and once it quenches to the ground state, it is directed away from the CI. When the intersection is sloped however, the quenched wave packet is not strongly directed away from the intersection. In fact, one easily sees that it may recross back to the excited state. If the wave packet crosses the CI only once, a single photoproduct (11-*cis* in the case of RPSB) will be formed. On the other hand, if the wave packet funnels down and up (i.e., crosses from S1 to S0 and then back) many times, the distribution of photoproducts will become statistical (i.e. half 13-*cis* and half back to all-*trans*). Detailed simulation of the quantum mechanical dynamics is needed for a quantitative prediction of the product branching ratios. Nevertheless, a simple estimate based on the above considerations is in qualitative accord with the experimental data, 2:1 for 11-*cis* relative to 13-*cis* compared to experimental results which range from 2:1 to 8:1 depending on solvent and excitation wavelength.

NAMD: Scalable Molecular Dynamics Software

NAMD is a parallel, object-oriented molecular dynamics code designed for high performance simulation of large biomolecular systems [25]. NAMD is distributed free of charge via the web* as both source code and convenient precompiled binaries for massively parallel supercomputers, workstation clusters, and personal computers. NAMD has over 1700 registered users who have downloaded the program over 3700 times during the past year. NAMD is also distributed with the Scyld Beowulf advanced Linux cluster operating system and is installed at the three NSF supercomputer centers (PSC, NCSA and SDSC). The excellent scalability and performance of NAMD was recognized by our selection as a finalist for the 2000 Gordon Bell Awards.†

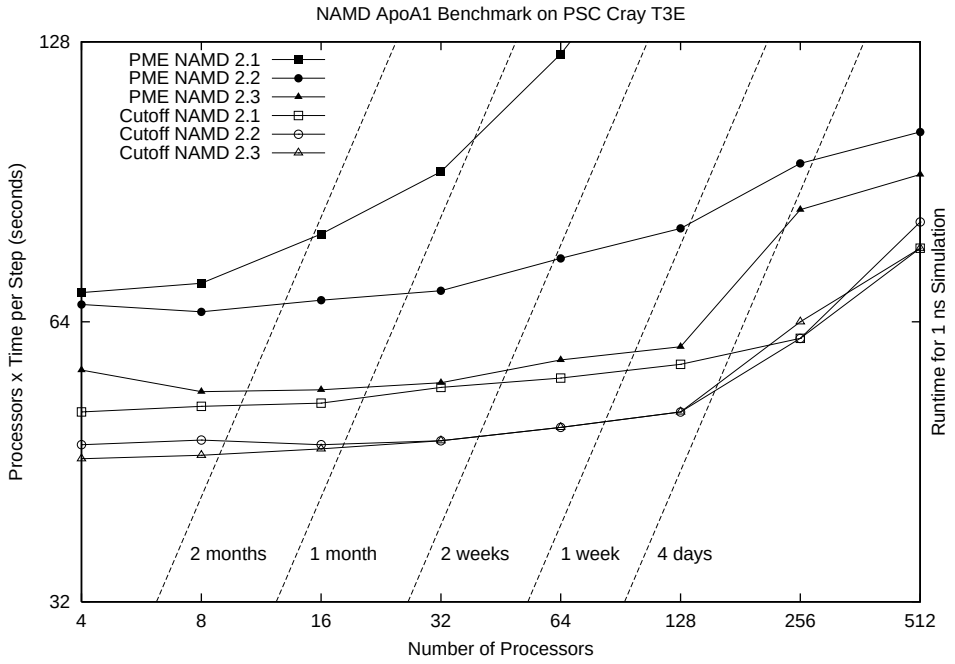

Figure 3: Total resources consumed per step for 92K atom benchmark with and without particle mesh Ewald by NAMD versions 2.1–2.3 on varying numbers of processors. Perfect linear scaling is a horizontal line. Diagonal scale shows absolute performance.

NAMD 2.2, released in September 2000, featured a newly parallelized particle-mesh-Ewald reciprocal space sum, eliminating a major serial bottleneck which had limited the scalability of simulations employing full electrostatics. While this grid-based calculation accounts for a small fraction of overall runtime, when parallelized it has much higher communication requirements than the complementary short-range force evaluation. The NAMD design, which employs the prioritized message-driven execution capabilities of the

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

†URL: `http://www.sc2000.org/techpapr/index.htm#15`

Charm++/Converse parallel runtime system,[‡] interleaves the reciprocal space sum with other available work to keep all processors busy while waiting on large data transfers. The resulting performance increase is illustrated in Figure 3.

Until recently, the NAMD project has sought only to complement existing molecular modeling software such as X-PLOR [26] and CHARMM [27] by providing an alternate engine for efficient parallel simulation. However, user feedback has demonstrated the demand for a more complete modeling environment which is easy to use and freely available. NAMD 2.3, released in April 2001, includes the *psfgen* utility for generating molecular structures from standard PDB coordinate files and the topology definitions supplied with the CHARMM force field. User demand for extensions and modifications to this standalone program is strong, and its modular design based on the Tcl scripting language will allow the graceful addition of new capabilities.

Refinement of the critical "inner loop" code in NAMD has led to significant performance increases during the past year. The costly evaluation of transcendental functions used in Ewald calculations has been eliminated. A smooth and highly accurate approximation to the electrostatic interatomic potential and gradient is now determined by interpolation from a lookup table, resulting in up to a 50% total performance increase in NAMD 2.3. The associated code simplification, combined with the elimination of branching, also allowed software pipelining optimization on the highly compiler-dependent Intel IA64 Itanium processor, more than doubling NAMD performance.

Ongoing porting and tuning efforts ensure that NAMD users benefit immediately from the availability of new parallel platforms. In the past year, NAMD has been ported to the IBM SP, Compaq AlphaServer SC at PSC, VMI-based Linux clusters at NCSA, cost-effective Scyld Beowulf clusters for laboratory use, Alpha Linux, Windows, and Mac OS X. We have been aggressive, working with NCSA and PSC, to optimize NAMD for their new teraflop platforms before they were made generally available. This provided our local users with "friendly user time" allocations which have been used for unprecedented simulations of up to 400,000 atoms. In collaboration with NCSA and Intel we ported NAMD to both Windows and Linux on the new Intel IA64 architecture.

In the coming year we will implement AMBER [28] compatibility, incorporate alchemical free energy perturbation calculations into NAMD, and extend the structure building and analysis capabilities of psfgen. We will improve the scaling of NAMD on new teraflop clusters at NCSA and PSC, and educate our user community about the excellent performance of NAMD on low-cost Linux clusters.

[‡]URL: `http://charm.cs.uiuc.edu/`

Interactive Molecular Dynamics

The binding properties of biomolecules and their response to mechanical forces can now be studied directly using single-molecule micromanipulation experiments. The insight gained by these investigations has inspired us and others [29–31] to adopt a similar approach for the study of biomolecules by means of computer simulations. One such simulation approach, termed Steered Molecular Dynamics (SMD) [32], has already provided important qualitative insights into biologically relevant problems, including identification of binding pathways and the explanation of elastic properties of proteins at supercomputing facilities. With modern high-performance workstations, SMD can be implemented as an interactive system, rather than in batch mode. Such an arrangement permits the user to make adjustments to the applied forces based on the progress of the simulation. We term this approach Interactive Molecular Dynamics (IMD). *

Our goal for IMD is to provide real-time feedback and steering for molecular dynamics simulations of biomolecules. Force feedback in particular will enhance the already substantial insight that can be gained from SMD. Incorporating force feedback poses a signficant challenge to an IMD system; therefore, we began with software designed to handle large, complex biomolecular systems.

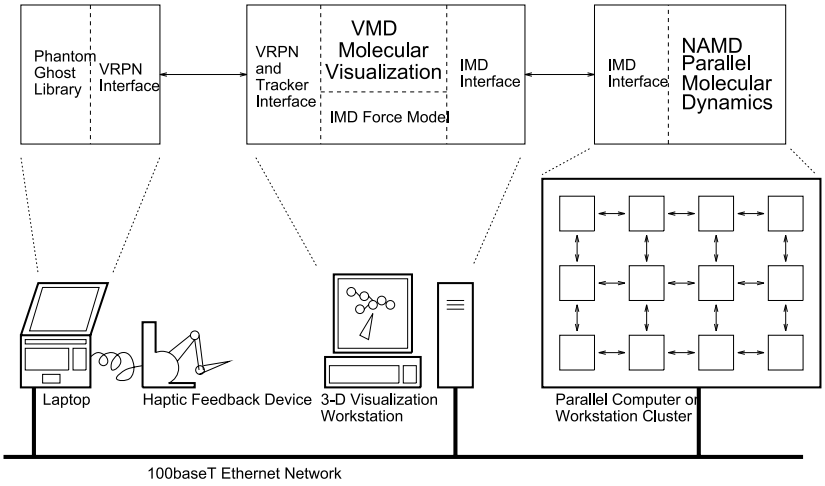

Figure 4: Decomposition of IMD components into asynchronous communicating processes.

IMD consists of three primary components (see Fig. 4): a haptic device which provides translational and orientational input as well as force feedback to the user's hand; molecular dynamics simulation for determining the effects of force application, and a visualization program for display of the results. IMD requires efficient network communication

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

between the visualization front-end and the molecular dynamics back-end. While the network bandwidth requirements for performing IMD are quite low relative to the computational requirements, latency is a major concern. IMD uses custom sockets code to allow VMD and NAMD to communicate efficiently. The entire IMD interface consists of a small set of C-callable functions which can be adapted to any molecular dynamics and/or visualization programs. An IMD interface was recently written for the ProtoMol [33] molecular dynamics framework.

Each time through its event loop, VMD checks for a coordinate set from the MD program, updates the representation geometry if a new coordinate set was received, redraws the screen, and updates the restraint position of the haptic device. If the user has applied a force through the haptic device, VMD routes this force to NAMD, which then integrates the force into the equations of motion for the molecule. VMD communicates with a server provided by the VRPN library [34]; the server controls the haptic environment experienced by the user handling the device. Updates to the haptic restraint point are made when VMD receives a new coordinate set from NAMD; while awaiting an update, the haptic server applies smooth feedback forces based on the most recent restraint point position. This scheme of splitting the haptic, visualization, and simulation components into three communicating, asynchronous processes has been employed successfully elsewhere [35].

We have developed a model of the forces experienced by the user during an IMD session. An important insight obtained from the model is that simulated atoms tugged by the haptics device have an effective mass which depends quadratically on the speed of the simulation. The effective mass can be made smaller by scaling up the force applied by the user. However, this cannot be done without limit since the applied forces will overwhelm the forces due to the simulation potential. The user would not be able to feel the potential, only the response of the particle restrained by the haptic device. Finally, atomic coordinates are scaled up in order to be perceptible to humans. This factor is ultimately limited by the workspace of the haptic device, although one could in practice focus on a small part of the simulation region in order to increase the effective spatial resolution of the haptic interface.

Our current implementation of IMD has shown that it is important to minimize sources of latency and unnecessary synchronization between the components of the system. The existing decomposition of the IMD components into three concurrent communicating processes was sufficient for our early investigations into IMD, however a finer-grained decomposition utilizing multithreading could provide further reductions in communications latency and entirely eliminate the remaining synchronization of haptic constraint updates with visual display. With these improvements in place, only the coordinate update rate of a given molecular dynamics simulation would limit the sensitivity of the haptic device

and the overall performance of the IMD system.

BTA UNIT: C,T

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

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

AXIS I: 2,7a

AXIS II: 74f,h; 77

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DEPT1: Physics
NONHOST1:

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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 [1] as well as mammals [2, 3]. 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 [4], paving the way for the crystal structure [36] of MscL from *M. tuberculosis* (Tb-MscL). These proteins all produce a channel activity in response to membrane tension alone.

Molecular dynamics simulations of Tb-MscL [37] have hinted at a gating mechanism which involves flattening of the transmembrane helices, followed by opening of the central pore. Sukharev et al. [10] have put forth a model of MscL gating, based on molecular modeling, patch-clamp, and cysteine cross-linking studies; this model suggests that residues 1-9 in each subunit, which were unresolved in the MscL crystal structure [36], play a critical role as the gate in the channel.

We have begun simulations of Tb-MscL using applied surface tension boundary conditions to induce gating in the channel. We have also begun steered molecular dynamics simulations of the N-terminal bundle of residues as modeled by Sukharev et al. [10] in order to elucidate their role in channel gating. Preliminary results suggest a two-stage model for opening, involving both transmembrane helices and the N-terminal bundle. As membrane tension is applied, both membrane and protein become thinner; the resulting tilting of the transmembrane helices tugs on the N-terminal bundle, causing channel gating. Further simulations will investigate this

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

process further through equilibrium simulation of the open channel, steered molecular dynamics simulations [38] of the N-terminal bundle, and simulations of a model of MscL from *E. coli*.

BTA UNIT: T

TITLE: The Role of Intersection Topography in Bond Selectivity of cis-trans Photoisomerization

KEYWORDS: retinal protonated Schiff base, cis-trans isomerization, photochemistry, conical intersections, bond selectivity

AXIS I: 2

AXIS II: 77

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% BRTP $: 3%

ABSTRACT: Photoinduced *cis-trans* isomerization represents one of the simplest means to convert light into mechanical motion at the atomic scale, and is widely used in photoactive proteins. Retinal protonated Schiff base (RPSB) is the best known biological chromophore, with five double bonds capable of undergoing photoisomerization. A long-standing question has been the mechanism that selects the bond which isomerizes, particularly the role of the protein environment in "steering" reactivity. Availability of the structures of rhodopsin [11] and bacteriorhodopsin [12–14, 14, 39] coupled with characterization of RPSB solution-phase photochemistry [15–20] provides a unique opportunity to identify this mechanism. Although conical intersections (CIs) - configurations where two electronic states are truly degenerate, providing doorways from excited to ground electronic states - are widely believed to be important in photochemistry [21, 40, 41], their role in bond torsion selectivity has yet to be established.

Using accurate *ab initio* quantum chemistry methods and a realistic chemical model, we have investigated the origin of bond selectivity of RPSB in solution. We have found that in RPSB the two minimal energy CIs relevant for isomerization around the C_{13}=C_{14} and C_{11}=C_{12} bonds are isoenergetic and both coincide with a twisted local minimum on the excited electronic state. However, the local topography of the two CIs is qualitatively different, and is consistent with the observed preference for the 11-*cis* photoproduct in solution. This is the first time that a direct connection between CI topography and photochemical selectivity has been made for any molecule, with significant implications for understanding protein "steering" and the mechanism of vision.

BTA UNIT: T, D

TITLE: NAMD: Scalable Molecular Dynamics Software

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

AXIS I: 9

AXIS II: 42, 89

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% BRTP $: 12%

ABSTRACT: NAMD is a parallel, object-oriented molecular dynamics code designed for high performance simulation of large biomolecular systems [25]. NAMD employs the prioritized message-driven execution capabilities of the Charm++/Converse parallel runtime system,* allowing excellent parallel scaling on both massively parallel supercomputers and commodity workstation clusters. NAMD is distributed free of charge via the web† to over 1700 registered users as both source code and convenient precompiled binaries.

NAMD 2.2 was released in September 2000 and features:

- ports to the IBM SP, Alpha Linux, and Windows,
- improved parallelization of particle mesh Ewald,

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

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

- a faster minimizer based on the conjugate gradient method, and
- an improved load balancer for scaling to over 1024 processors.

NAMD 2.3 was released in April 2001 and features:

- ports to the Compaq AlphaServer SC at PSC, Scyld Beowulf, VMI Linux clusters at NCSA, and Mac OS X,
- a new tool *psfgen* for building PSF structure files,
- simpler execution on single workstations, and
- up to 50% faster serial performance due to improvements in particle mesh Ewald.

We have been aggressive in working with NCSA and PSC to optimize NAMD for their new teraflop platforms before they were made generally available. In collaboration with NCSA and Intel we ported NAMD to both Windows and Linux on the new Intel IA64 architecture.

In the coming year we will implement AMBER [28] compatibility, incorporate alchemical free energy perturbation calculations into NAMD, and extend the structure building and analysis capabilities of psfgen. We will improve the scaling of NAMD on new teraflop clusters at NCSA and PSC, and educate our user community about the excellent performance of NAMD on low-cost Linux clusters.

BTA UNIT: T, D

TITLE: Interactive Molecular Dynamics

KEYWORDS: molecular dynamics, molecular visualization, haptic feedback

AXIS I: 9

AXIS II: 42, 89

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ABSTRACT: The binding properties of biomolecules and their response to mechanical forces can now be studied directly using single-molecule micromanipulation experiments. The insight gained by these investigations has inspired us and others [29–31] to adopt a similar approach for the study of biomolecules by means of computer simulations, termed Interactive Molecular Dynamics (IMD). * Our goal for IMD is to provide real-time feedback and steering for molecular dynamics simulations of biomolecules. Force feedback in particular will enhance the already substantial insight that can be gained from SMD.

Incorporating force feedback poses a signficant challenge to an IMD system; therefore, we began with software designed to handle large, complex biomolecular systems. Our IMD implementation uses VMD [42] for visualization, NAMD [25] for molecular dynamics, and the VRPN library [34] running on a laptop to control the haptic device. All three components communicate over fast ethernet. This scheme of splitting the haptic, visualization, and simulation components into three communicating, asynchronous processes has been employed successfully elsewhere [35].

Experiments with test systems of approximately 4000 atoms have allowed us to develop an effective user interface for IMD. We have also developed a model of

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

the forces experienced by the user during an IMD session. An important insight obtained from the model is that the responsiveness of the simulation to haptic input goes as the square of the simulation speed. Finally, multithreaded communication between VMD and NAMD, as well as other software improvements, have greatly increased the efficiency of the IMD connection, making interactive simulation of larger systems practical [43].

Future plans for IMD include addition of torque feedback and support for multiple haptic devices, which will be important for docking applications.

BTA UNIT: C

TITLE: Spectral tuning in retinal proteins

KEYWORDS: spectral tuning, rhodopsin, retinal, Schiff base, QM/MM, excitation energy

AXIS I: 7a, 25b

AXIS II: 74h, 89

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ABSTRACT: The rhodopsin family of receptors consist of an apoprotein (opsin) and a retinal chromophore covalently bound to it by a protonated Schiff base linkage to a lysine residue. While the protonated retinal Schiff base absorbs at about 440 nm in organic solvents, its maximal absorption (λ_{max}) is drastically changed after binding to the apoprotein, an effect known as 'opsin shift'. Observed absorption maxima of the same chromophore range from 360 to 635 nm. A fundamental challenge in vision research has been the elucidation of the physical mechanism by which the protein matrix adjusts λ_{max} of the chromophore, using the molecule retinal to detect light at different wavelengths.

The mechanism of spectral tuning in the rhodopsin family of proteins has been investigated by means of a combined *ab initio* quantum mechanical / molecular mechanical technique. Calculations are performed on two archaeral rhodopsins, for which crystal structures with high resolutions are available. Dispite a high degree of similarity in the three-dimensional structure, electrostatic environments in these proteins differ sufficiently to shift the absorption maxima of their common chromophore. This spectral shift, involving the electronical ground (S_0) and first excited (S_1) states of retinal, is predicted correctly within 10 nm by the calculations. The spectral shift can be predominantly attributed to a change in polarization of the S_1 state. A second, weakly allowed excited state, S_2, is predicted to lie energetically close to S_1. Its energetic proximity to the S_1 state suggests strong vibronic coupling that could explain that the S_2 state manifests itself through a shoulder observed in the spectrum. The successful explanations of the spectral shift opens the door to investigations that seek to explain on the basis of *ab initio* quantum chemical calculations the spectral tuning and basis of color vision in visual pigments.

BTA UNIT: T, C

TITLE: Molecular basis of the function of rhodopsin

KEYWORDS: G-protein coupled receptors, photocycle, membrane protein, retinal

AXIS I: 9,25

AXIS II: 42,74h,77

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ABSTRACT: G-protein coupled receptors (GPCR) are the most important family of membrane receptors in mammalian cells, and detect a variety of extracellular signals, including different hormones, a wide range of neurotransmitters, odors, and visual signals. After several years of efforts, the first X-ray structure of a GPCR, bovine rhodopsin (Rh) *, has been solved. The availability of the structure of Rh [44] enabled us to start a systematic approach toward the study of the function of this protein. A large body of structural and biochemical work on Rh has indicated conformational changes in the protein matrix surrounding the retinal, during the photocycle. How such changes in Rh lead to the activation of G-proteins is not exactly known. In order to study the mechanism of activation in Rh several molecular dynamics simulation were performed. The CHARMM energy function, and the program NAMD2 (www.ks.uiuc.edu/namd) were used for MD simulations.

Comparison of the MD simulations performed with different constraints showed that, even in the absence of a lipid bilayer, Rh is stable in the 1 nanosecond time scale of the simulations. In order to study the effect of retinal unbinding, which is the activation mechanism, simulations were repeated after removal of the retinal moiety. The results clearly indicate a series of conformational changes in several aromatic amino acids, which are very similar to the proposed mechanism of G-protein activation in another GPCR. We have also studied the role of the disulfide bond between Cys110 and Cys187 residues on the structure of Rh. This bond, which is a common feature in GPCRs, seems to stabilize the structure of the E-II loop in Rh. Our simulations, however, indicate that after breakage of this bond, a large conformational change occurs in the region close to the binding pocket of the chromophore. In order to exclude artificial effects, this simulation has to be repeated in the protein-membrane model.

We are now embedding the protein in a lipid bilayer membrane. After complete equilibration, this model will be used for the study of the photoisomerization event and the consequent conformational changes in Rh.

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

BTA UNIT: T, C

TITLE: Energy Conversion in the Transmembrane F_o Unit of ATP Synthase

KEYWORDS: Bioenergetics, energy conversion, ATP hydrolysis, ATP synthesis, proton transfer, structural group movement, electrostatic interactions, molecular motor, membrane proteins, membranes, molecular dynamics

AXIS I: 2

AXIS II: 89

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% BRTP $: 3%

ABSTRACT: Adenosine triphosphate (ATP) synthase is a large membrane protein, which performs energy conversion in living cells, synthesizing or hydrolyzing ATP, the ubiquitous energy carrier. ATP synthase converts the energy of the transmembrane proton gradient into the mechanical energy of the central stalk rotation, which then drives formation of phosphoanhydride bonds in ATP synthesis. ATP synthase can work in the reverse direction, hydrolyzing ATP and utilizing the released energy to pump protons across the membrane. This reversibility, along with the nearly 100% efficiency of hydrolysis and the recently discovered, remarkably symmetric structure, makes ATP synthase a perfect object for exploring molecular mechanisms of interconversion between mechanical and chemical energy in molecular motors.

We used molecular dynamics (MD) techniques to investigate the energy conversion mechanisms on the atomic scale. We performed MD simulations with a focus on the following events: domain motion at the catalytic sites in the process of ATP synthesis/hydrolysis, torque transmission by the central stalk, and domain motion within individual subunits and the whole transmembrane segment accompanied by proton translocation. Because of the large size of an ATP synthase molecule, we employed the steered MD (SMD) methods to put the relevant time and force scales within reach. The calculations were performed using the highly scalable MD program

NAMD, developed in the Theoretical Biophysics Group and extensively tested on a broad variety of platforms including supercomputers. The calculations were done in collaboration with leading experimental groups (Fillingame, Wisconsin; Junge, Germany; Wilce, Austrailia).

BTA UNIT: T

TITLE: Central stalk rotation in F_1 ATP synthase

KEYWORDS: Bioenergetics, energy conversion, ATP hydrolysis, ATP synthesis, elastic, mechanical, structural group movement, electrostatic interactions, molecular motor, molecular dynamics

AXIS I: 2

AXIS II: 74h, 89

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ABSTRACT: The proton gradient-driven rotation of the F_o subunit of ATP synthase causes rotation of the central stalk of the F_1 subunit. The rotating central F_1 stalk [45,46] in turn causes comformational changes in the surrounding α and β subunits that lead to generation of ATP from ADP and P_i. During the past twelve months, we initiated SMD investigations of the elastomechanical properties of subunit F_1*, in order to identify interactions between the central stalk and the surrounding α and β subunits, and mechanisms of resulting conformation changes.

For these simulations, the F_1 structure was built from coordinates of DCCD-inhibited bovine mitochondrial ATP synthase [47], which has a nearly complete central stalk: the δ and ϵ chains are contiguous, and the γ chain is contiguous except for residues 62–66 and 97-100.The missing loops of the γ subunit were modeled in place: first as a poly-glycine chain fitted into the correct position, and after several visual manipulations mutated stepwise to the corresponding residues; following this the system was subjected to rounds of minimization and equilibration. Nucleotides and magnesium ions were added, then the system was placed in an enclosing water box with solvating ions and further equilibrated. The assembled system included 327,500

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

atoms. Torque was applied to the system by applying "constant rotational velocity" restraints in the solvent-exposed section of the central stalk, while the 3 C_α atoms at the α subunit N-termini were held fixed. Forced rotation simulations are in progress, at 30 rev/ns and 1 rev/ns rotation speeds; a 0.05 rev/ns simulation is planned to examine hydrogen bonding near ATP binding sites.

BTA UNIT: T

TITLE: Excitation migration in photosynthesis

KEYWORDS: photosynthesis, purple bacteria, Förster theory, master equation

AXIS I: 7a

AXIS II: 74h, 89

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% BRTP $: 2%

ABSTRACT: Purple bacteria have developed an efficient apparatus to harvest sunlight*. The apparatus consists of up to four types of pigment-protein complexes: (i) the photosynthetic reaction center surrounded by (ii) the light-harvesting complex LH1, (iii) antenna complexes LH2, which are replaced under low-light conditions by (iv) antenna complexes LH3 with a higher absorption maximum. Following absorption of light anywhere in the apparatus, electronic excitation energy is transferred between the pigment-protein complexes until it is used for the primary photoreaction in the reaction center.

We calculated, using Förster theory, all rates for the inter-complex excitation transfer processes [48] on the basis of the atomic level structures of the pigment-protein complexes and of an effective Hamiltonian, established previously [49], for intra-complex excitations. The kinetics of excitation migration in the photosynthetic apparatus can be described through a master equation which connects the calculated transfer rates to the overall architecture of the apparatus. For two exemplary architectures, we determined the efficiency, distribution of dissipation, and time evolution of excitation migration [48]. Pigment-protein complexes were found to form an excitation reservoir, in which excitation is spread over many chromophores rather than forming an excitation funnel in which excitation is transferred without

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

detours from the periphery to the RC. This feature permits a high quantum yield of 83 % to 89 %, but also protects the apparatus from overheating by spreading dissipation over all complexes. Substitution of LH2 complexes by LH3 complexes or choice of an architecture in which all LH2 (LH3) complexes are in contact with LH1 to an architecture in which few LH2 (LH3) complexes are in contact with LH1 increases the quantum yield up to 94 % and decreases the degree to which disspipation is evenly distributed.

BTA UNIT: C

TITLE: Gold binding protein

KEYWORDS: biomineralization, gold, molecular dynamics

AXIS I: 2

AXIS II: 74h

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% BRTP $: 2%

ABSTRACT: The biological control of inorganic crystal morphology is necessary for the formation of biological hard tissue and of use in the creation of novel materials. Sarikaya et al. have developed a genetic system to isolate proteins which control gold crystalization. It was shown [50] that in the presence of gold binding protein (GBP)*, gold formed large, flat hexagonal crystals displaying the {111} surface. No such crystals were seen to form in the presence of control proteins which do not bind to gold.

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

We have predicted structures for the three GBP sequences available using sequence similarity methods in addition to the Holley-Karplus prediction method [51] implemented in Quanta [52]. Of the three proteins, two are seen to have repeating motifs which may be conducive to binding to a periodic surface. Molecular dynamics simulations lasting five nanoseconds of fully solvated GBP on both the {111} and {112}

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

crystal surfaces ($\sim$ 30000 atoms) have been carried out using NAMD [53]. The dynamics show that the close contacts to gold originate from the polar sidechains. Additionally, water is found to diffuse in the surface corrugations of the {112} surface, hindering the interaction.

BTA UNIT: T

TITLE: Multi-resolution modeling of protein-DNA interactions

KEYWORDS: protein-DNA interactions, gene expression, multi-resolution modeling, *lac* repressor, theory of elasticity

AXIS I: 2,7,9

AXIS II: 42,74g,77,89

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% BRTP $: 2%

ABSTRACT: During the past funding year, the development of a multi-resolution approach to modeling protein-DNA interactions has been continued. Protein-DNA interactions underlie the core process of life - the expression of genetic information - and successful modeling of this process is essential for our understanding of life. The sizes of biomolecules and time scale of events involved in protein-DNA interactions span several orders of magnitude; therefore, a multi-resolution approach is essential for effectively modeling the genomic expression.

The developed modeling method employs a coarse-grained elastic rod model* to describe long DNA loops and an all-atom model to describe the proteins binding to the DNA. We improved the previously developed coarse-grained model by implementing a new, faster and more robust algorithm for solving the integro-differential equations of elasticity resulting from adding the electrostatic self-repulsion term. The dependence of the problem solution on the problem parameters was systematically studied for the case of a 76 bp DNA loop clamped by the *lac* repressor [54]. The shape of the loop was shown to be mainly defined by the boundary conditions, whereas the energy of and the stress inside the loop depended heavily on

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

the anisotropy of DNA flexibility. The electrostatic self-repulsion was shown to be significant only in such cases when the DNA loop has points of near self-contact.

The problem was solved for a longer 385 bp DNA loop, which can also be induced by the *lac* repressor binding to the *E.coli* genome [54]. Four solutions of different topology were found in this case. However, only one of the four DNA loop structures should be predominant under natural conditions, because its energy is significantly lower than that of the others.

The next step in the development of the multi-resolution modeling method is to study the changes in the structure of the *lac* repressor caused by the stress of the looped DNA. We built an all-atom structure of the *lac* repressor-DNA complex using several existing x-ray and NMR structures of parts of this protein-DNA complex. A solvation cell was built around the complex; the electrostatic potential of the solvated protein-DNA system has been systematically studied in order to optimize the size of the cell. The final all-atom system includes 190,000 atoms. The simulations of it will be performed in periodic boundary conditions, using constant pressure and temperature algorithms, and full electrostatic interactions. The forces from the clamped DNA loop, computed using the coarse-grained model, will be applied to the protein-bound DNA segments and regularly updated in order to reflect changes in the orientation of those segments.

BTA UNIT: C

TITLE: Mechanical properties of titin

KEYWORDS: titin, folding, refolding, immunoglobulin, SMD

AXIS I: 13,20

AXIS II: 74h

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% BRTP $: 3%

ABSTRACT: Immunoglobulin-like (Ig) domains constitute the basic elastic elements of titin, the longest covalently linked protein. Mechanical properties of these Ig modules have been revealed recently by AFM experiments [55, 56]. We employed steered molecular dynamics (SMD) to simulate the forced unfolding of immunoglobulin domain I27 [57–59] *. The SMD studies, along with the AFM experiments, demonstrated a water-involving scenario of the concurrent breaking of certain interstrand hydrogen bonds, which possibly determines the mechanical stability of the domains [60].

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

Partially unfolded intermediates of I27 were identified and further confirmed by site-directed mutagenesis and AFM experiments [61].

Extending the previous studies, molecular dynamics was applied to simulate the refolding of partially unfolded I27 domains [38]. The simulations revealed that the stretched I27 domains with ruptured interstrand hydrogen bonds shrank along the extension direction. Two types of refolding patterns were determined: five of the six hydrogen bonds, which provide most of the domain protection against force-induced unfolding, reform in less than 200 ps; whereas three hydrogen bonds, which provide the domain with a flexible extension, do not exhibit stable reformation on a 2 ns time scale. Mechanical stability of the partially refolded intermediates was tested by restretching using the constant force protocol of SMD; the revealing force versus extension profiles resemble closely those we observed previously in stretching native I27 domains.

Ongoing SMD simulations of I1 (for which a structure recently becomes available) and I27, solvated in a large water box (90,000 atoms), will further examine the mechanical properties of I27 intermediates during the late stage of unfolding.

BTA UNIT: C

TITLE: Aquaporin-1 (AQP1) water channel simulations

KEYWORDS: AQP1, aquaporin, water channel, molecular dynamics

AXIS I: 2

AXIS II: 74h

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% BRTP $: 2%

ABSTRACT: Aquaporin-1 (AQP1) is an important channel protein in cell membranes. It is abundant in many human tissues, such as red blood cells and renal proximal tubules. This protein furnishes fast water conductivity and high selectivity against ions (including protons) and other solutes. AQP1 has been studied for many years, but not until October 2000 was its first atomic structure determined and published [62]. The availability of the structure allowed us to conduct molecular dynamics simulations to further reveal the mechanism of this water channel.

In our study, the protein was embedded in a POPC lipid bilayer, then solvated and equilibrated. The whole system contains about 60,000 atoms. The simulations were carried out under constant temperature and pressure conditions, and full electrostatic calculation under periodic boundary conditions was achieved by using the Particle Mesh Ewald (PME) algorithm. The visualization software VMD [42] was used to set up the system and analyze the trajectories. For molecular dynamics simulations software NAMD2 [25] was used for all the simulations in this project.

We plan to apply steered molecular dynamics (SMD) [59] to investigate the dynamic process of the passage of water through the channel.

BTA UNIT: C

TITLE: Aquaglycoporin (GlpF), glycerol channel simulations

KEYWORDS: Aquaglycoporin, glycerol facilitator, Glpf, molecular dynamics

AXIS I: 2

AXIS II: 74h,89

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% BRTP $: 1%

ABSTRACT: Aquaglycoporin, (*E. Coli* glycerol facilitator, Glpf), a membrane channel protein, is a member of the aquaporin (AQP) family. All AQPs are capable of transporting water across the cell membrane and excludes ions and charged solutes. Human family members include at least 10 AQPs where AQP3, AQP6 and AQP9 are all permeable to glycerol. As culmination of several years of study, structures of two AQPs were recently reported, the human AQP1 [62] and the *E. coli* Glpf [63] structures. The 2.2. Å resolution of the Glpf structure included positions of glycerol and water molecules inside the channel making Glpf very amenable to molecular dynamics studies of the transport mechanism of glycerol and water.

For the molecular dynamics studies Glpf was embedded in a hydrated lipid bilayer using the software VMD [42]. The resulting system, about 106,000 atoms, was equilibrated under constant temperature and pressure using the program NAMD2 [25] and carrying out full electrostatic calculations. Spontaneous conduction of glycerol was observed due to thermal fluctuations and we could describe a full conduction event of a single glycerol passing through Glpf. Further examination

revealed a conduction pathway explaining the conserved secondary structure in Glpf (and possibly other AQPs). From simulations on Glpf without glycerol we can propose why Glpf (and possibly other AQPs) can conduct water but cannot conduct protons.

Systems are prepared for steered molecular dynamics (SMD) [32] in order to characterize the energetics of glycerol and water transport in Glpf. Interactive molecular dynamics (IMD) [43] investigations are also planned for Glpf.

BTA UNIT: T

TITLE: Dynamic dissorder in light harversting proteins

KEYWORDS: Dynamic dissorder, exciton, polaron, absorption spectrum

AXIS I: 2, 7a

AXIS II: 74c,f,h

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% BRTP $: 3%

ABSTRACT: A combined molecular dynamics/quantum chemistry (MD/QC) approach has been used to study the effect of dynamic disorder, at room temperature, on the electronic excitations of the B850 bacteriochlorophyls (BChls) in the light harvesting antenna complex LH-II of purple bacteria *Rs. molischianum*. In this novel approach, the dynamics of the nuclear degrees of freedom are treated classically, by using MD simulations, while the electronic excitations of B850s are calculated at every timestep quantum mechanically. The simulated system consisted of a LH-II ring embedded in a lipid bilayer, and it was fully solvated (87,055 atoms). The MD simulations were performed with NAMD2 [25] on the SGI Origin 2000, incorporating periodic boundary conditions and full electrostatics via PME. The QC calculations were done with the quantum chemistry package Gaussian98 [64].

The results of the simulations have been used to describe the B850 BChls, surrounded by the protein matrix, lipid bilayer and solvent molecules, in terms of a *polaron model*, consisting of exitons, coupled to a bath of phonons. The calculated absorption spectrum of the B850 BChl ring, based on our computer simulations and polaron model approaches, is found to be in good agreement with recent experimental results [65].

Currently we are extending our polaron model of the B850 excitons by employing a more accurate phonon spectrum, extracted from the results of our computer simulations.

BTA UNIT: T

TITLE: Stochastic quantum mechanics of light harvesting proteins

KEYWORDS: photosynthesis, light-harvesting complexes, purple bacteria, random matrix theory, spectral universality

AXIS I: 7a, 9

AXIS II: 74h, 77, 89

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% BRTP $: 3%

ABSTRACT: Photosynthetic bacteria provide relatively simple examples for the study of photosynthesis when compared to higher plants. The photosynthetic apparatus of purple bacteria contains several hundred chromophores (pigments) per reaction center, which are organized in ring like structures. One of the associated protein-pigment complexes, LH-II, exhibits an 8-fold symmetry in the case of *Rhodospirillum (Rs.) molischianum* [66] and a 9-fold symmetry in the case of *Rhodopseudomonas (Rps.) acidophila* [67]. In *Rs. molischianum*, LH2 contains 8 lycopenes, 8 B800 bacteriochlorophylls (BChls) and 16 B850 BCHls. The B850 ring is packed closely enough to warrant a formulation in terms of an effective (16×16) Hamiltonian describing collective electronic excitations of the system. The study of the spectral properties of this effective Hamiltonian is essential for a better understanding of the light absorption process.

A random matrix model describing this effective Hamiltonian in the presence of static disorder has been constructed. An important question is about the role of the the particular choice of the disorder term. We have observed through entensive numerical studies, that the spectral characteristics of bacterial light-harvesting complexes, especially the absoprtion spectrum itself, is largely independent of the choice of the distribution of the disorder term and only the overall width of the distribution plays a significant role. This is reminiscent of the universality theorems known in random matrix theory. Also, using the framework of random matrix theory we have been able to obtain analytically, the spectral density in the presence of a disorder term described by a unitary ensemble. This kind of an analytical understanding can be applied to similar pigment-protein complexes, and it is complementary to both experimental and computational studies of these systems.

BTA UNIT: T

TITLE: Monte Carlo studies of DNA loops in protein-DNA complexes

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

AXIS I: 7a, 9

AXIS II: 58, 74g, 77, 89

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DEGREE2: M. Sc.
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% BRTP $: 2%

ABSTRACT: The study of protein-DNA interactions is essential for a better understanding of gene expression and the replication and storage of genetic material. Typically, the size of the protein-DNA complex renders an all atom study computationally unfeasible, requiring a coarse-grain description for DNA. Due to the elastic stability and the large persistence length (around $45nm$) of DNA, a suitable coarse-grained model can be built on the basis of the theory of elasticity.

We have developed a Monte-Carlo framework for the sampling of elastic conformations of DNA for a given set of boundary conditions at a given temperature. This allows us access to proper thermal distributions of physical variables, such as contact forces and tensions, which determine the stability and structural properties of a protein-DNA complex. We are currently applying this framework to one of the classical examples of gene regulation mechanisms, namely the *lac* repressor-DNA complex. The structure of this protein-DNA complex is known from crystallographic studies [54] and the structure of the DNA loop produced by the lac repressor was predicted using the theory of elasticity by research performed here at the resource [68]. The effect of a thermal fluctuations of the DNA-loop on the structure of the *lac* repressor is yet to be determined. A combined approach of real-time Monte-Carlo studies with molecular dynamics may prove essential for the understanding of such an effect.

BTA UNIT: C

TITLE: Mechanical properties of G-proteins

KEYWORDS: G-protein, force generation, GTP hydrolysis, molecular switch, molecular dynamics

AXIS I: 9

AXIS II: 74h, 84

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% BRTP $: 2%

ABSTRACT: The striking similarities between the nucleotide binding domains in GTP hydrolyzing G-proteins and ATP hydrolyzing motor proteins suggest that cell signaling G-proteins may also have mechanical activity. To investigate the mechanical force and work generating features of G-proteins, we developed a molecular dynamics (MD) simulation model for Ras, the smallest monomeric G-protein. Ras is of great medical interest, because activated forms of the Ras gene can be found in about 30% of all human tumors. Ras is a molecular switch which cycles between an inactive, GDP-bound state and an active, GTP-bound state. The main conformational difference between these two states is restricted to two regions (the so-called switch I and II regions) located at the interface of Ras and GAP, a regulatory proteins which catalyses GTP hydrolysis in Ras/GTP. A systematic MD study of the spontaneous conformational change following GTP hydrolysis, revealed that force generation by Ras is due to the equilibrium fluctuation between force generating substates of the relaxed Ras/GDP conformation, rather than the conformational change itself. The

MD simulations of the completely solvated Ras protein (∼20,000 atoms) were performed using periodic boundary conditions, at constant temperature and pressure.

In order to obtain a better understanding of force generation by G-proteins, we are currently investigating via MD simulations: (1) the effect of mutations of key amino acids in Ras (e.g., Gly60) on the conformational transition which leads to the force generating substates, and (2) the interaction between Ras/GAP after hydrolysis. Here the focus is to determine whether the force generated by Ras is sufficient to destroy the adhesion between Ras and GAP after hydrolysis, a step which is indispensable for the reactivation of Ras and the Ras signaling cycle.

BTA UNIT: T

TITLE: Photophysics of Green Fluorescent Protein Chromophore

KEYWORDS: green fluorescent protein, gene-tag, fluorescence, quantum chemistry

AXIS I: 2,9

AXIS II: 77

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INVEST2: Leslie Manohar
DEGREE2:
DEPT2: Department of Chemistry
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% BRTP $: 1%

ABSTRACT: The Green Fluorescent Protein (GFP) has become one of the most important fluorescent reporters in molecular biology. Because the chromophore is formed autocatalytically without any cofactors during folding, it is possible to use the methods of molecular genetics to co-express GFP along with any desired protein. One can then irradiate a cell or organism with blue light and determine where the protein of interest was expressed by mapping out the spatial profile of GFP fluorescence [69,70]. This can be done in vivo, without disturbing the normal biochemistry of an organism. One key goal that must be reached in order to extend the usefulness of this technique is the generation of mutants with different fluorescence wavelengths. This would enable tagging of multiple proteins in order to determine co-localization of protein expression [69,71]. Although progress has been made on this front, the detailed mechanism of GFP's photophysical behavior is not well understood, providing an obstacle to the rational development of a family of mutant GFP chromophores. We have used *ab initio* quantum chemistry to explore the ground and excited state potential energy surfaces of the chromophore. These studies have found several conical intersections at twisted geometries which explain the lack of fluorescence in the GFP chromophore in solution. We have also determined that the electrostatic characteristics of the protein environment do not play a major role in determining the absorption and emission wavelengths. Future work will model the dynamics of the chromophore in solution and protein environments directly.

BTA UNIT: T

TITLE: Photophysics of Photoactive Yellow Protein Chromophore

KEYWORDS: photoactive yellow protein, molecular signaling, quantum chemistry

AXIS I: 2

AXIS II: 77

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% BRTP $: 1%

ABSTRACT: The Photoactive Yellow Protein (PYP) is a useful paradigm for molecular signaling. The structure of the protein is accurately known, including several intermediates in the photocycle [72–75]. The fold of the active subdomain of the protein, known as the PAS domain fold, has been shown to be ubiquitous in signaling proteins, suggesting that many of the general characteristics of signaling may be embodied in PYP [76]. We have used ab initio quantum chemistry to explore the ground and excited state potential energy surfaces of the chromophore. We have found excellent agreement with the observed absorption and emission wavelengths in the protein, even though our calculations treat only the isolated chromophore. This suggests that the electrostatic environment of the protein does not play a major role in spectral tuning in PYP [77]. We have located conical intersections, which are expected to be important in determining the photochemical mechanism of the protein. Finally, we have found several local minima on the excited state potential energy surface that may be related to the early photocycle intermediates. Future work will model the dynamics of the chromophore in solution and protein environments directly.

BTA UNIT: T

TITLE: Reactive Fluctuating Charge Models for Biomolecular Dynamics

KEYWORDS: polarization, charge transfer, force fields

AXIS I: 2

AXIS II: 77

INVEST1: Jorge Morales
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% BRTP $: 1%

ABSTRACT: Force fields represent one of the most important determinants of accuracy in atomistic biomolecular modeling. Two key limitations of most existing force fields are the inability to describe polarization and charge transfer. Polarization has been established to contribute up to 20% of intermolecular interaction energies and biomolecular solvation energies [78]. Charge transfer is of key importance in the electron transfer processes that are the crux of the respiratory cycle. We have been working to develop new models for potential energy surfaces that allow for accurate treatment of polarization and charge transfer effects, without excessive computational cost. We have turned to an exploration of electronegativity equalization (EE) methods [22,79] in order to accomplish this goal. There are well-known problems with EE methods, including a complete breakdown when bonds are broken and a tendency to "polarization catastrophes." In particular, the polarizability of a large molecule can often be too large by an order of magnitude, severely limiting the application of these methods in the context of biomolecules [80]. In recent work [81], we have explored the relationship between grand canonical (GC) ensemble and EE theories for describing charge flow in molecules. We have introduced a new unifying approach to classical charge transfer theories based on valence bond (VB) theory and the maximum entropy (ME) method, which we call MEVB. We have shown how MEVB reduces to GC and EE theories with different choices for the definition of atomic partial charge. The MEVB approach provides a rigorous framework within which both improved classical models of charge transfer can be developed and a well-defined procedure for interfacing classical electrostatic models with quantum chemistry can be established.

BTA UNIT: T

TITLE: First-principles Dynamics of Photoisomerization

KEYWORDS: ab initio molecular dynamics, photochemistry, cis-trans isomerization, ethylene, conical intersections

AXIS I: 2

AXIS II: 77

INVEST1: Michal Ben-Nun
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% BRTP $: 1%

ABSTRACT: In both biological and man-made molecules *cis-trans* photoisomerization processes represent one of the simplest means for converting photon energy to mechanical motion. Ethylene is one of the smallest molecules in which this process can be studied, and may serve as a paradigm within which the isomerization photochemistry and photophysics of larger unsaturated hydrocarbons can be understood. We have recently investigated the photochemistry [82] and electronic spectra [83] of ethylene using first-principles quantum dynamics [84]. In this approach the electronic and nuclear Schrödinger equations are solved simultaneously as dictated by the quantum mechanical nuclear dynamics. The computational expense of the method prevented us from demonstrating convergence using a hierarchy of quantum chemistry calculations. Therefore, we have systematically characterized the ground and excited state potential energy surfaces (PESs) of ethylene with (high-level) conventional quantum chemistry methods, and assessed the accuracy of our dynamical calculations [85]. In agreement with the dynamical calculations we found that the twisted geometry is a saddle-point (and not a true minimum) and that the lowest points on the optically bright state are conical intersections - configurations where two electronic states are truly degenerate - and not true minima. Of these we have found two nearly isoenergetic intersections - the twisted/pyramidalized geometry which our dynamical simulations previously highlighted, and another which corresponds to ethylidene. The calculations have also identified a cascade of Valence/Rydberg conical intersections which the dynamical simulations did not show. Future dynamical studies will treat the Rydberg states properly and characterize the dynamics as the molecule descends through the manifold of Rydberg states.

BTA UNIT: C, D

TITLE: Computational Facility

KEYWORDS: parallel computing, visualization, network

AXIS I: 11

AXIS II: 42,89

INVEST1: Tim Skirvin

DEGREE1: B.S.

DEPT1: Theoretical Biophysics

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% BRTP $: 8%

ABSTRACT: Over the past year we have made four important changes to our computational facility*: replacing old desktop computers with 3D visualization workstations, upgrading our computation clusters, upgrading our network infrastructure and system servers, and developing new administrative tools to better manage our environment. These changes have allowed for us to both perform more and larger molecular simulations, and to more efficiently utilize our resources. The group currently has 45 local users, and approximately 100 users overall.

The last year has seen a significant increase in the number of 3D graphics workstations available to the Group. Last year we had 24 machines capable of viewing large molecules; this year we have 44 (an increase of 83%). This upgrade was made possible due to advances in PC graphics cards; for only a few hundred dollars per machine, we upgraded all of our existing Linux boxes, and converted machines obtained by retiring our older PC cluster. At this time, every researcher in the Group has access to a 3D-capable workstation at his or her desk.

Over the last year we have significantly increased our compute resources. We have acquired three new, fast, and cheap PC clusters. The new clusters are very simple to manage and easier to use; based on the Scyld Linux cluster management package, they cost only $30,000 for a 32-node system. By purchasing these clusters and retiring our old PC and HP clusters, we have increased our local computational resources by 211%, while also improving the utilization of our local resources from 40% to almost 85%. Further such clusters may be purchased in the future, given sufficient funding and demand.

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

On the back end, over the last year we have performed a general system upgrade of our core servers. First and most important, we have upgraded from half a terabyte to 1.5 terabytes of disk space, which is distributed to about 100 clients and backed up nightly. In order to accomodate this, we have upgraded both the number and the power of our core system servers, buying a pair of new Sun Enterprise 250 servers (bringing the total to five), upgrading our existing servers, and adding several smaller Sun servers for other services such as e-mail and web serving. For backups, we have added two new 22-tape changers, as well as developing a new backup system for better speed, higher performance, and lower cost. All services are handled by redundant servers, to minimize downtime and mitigate the effects of system failure. Over the next year we plan to upgrade several of the small Sun servers to improve system performance, but otherwise our systems are well suited for the next year's expansion.

Administration-wise, over the last year we have developed and implemented several tools for managing the Resource and its computers. Spearheaded by the development of the a shared database framenwork, we have created several easily managed and maintained databases - an internal Address Book, a Group Library for managing our book collection, an externally accessible database of Group Publications, a database of System Loads, separate Hardware and Software databases, and a Machine database for all of our computers. All of these databases are maintained using common tools developed by the Group System Administrator.

As in previous years, our group has been awarded computer time at National Science Foundation funded supercomputing sites by the National Resource Allocation Committee (NRAC). We have been awarded 5,000 service units on the SDSC Blue Horizon, 69,498 units on the PSC TCS1, 210,000 units on the NCSA Origin 2000, and 310,000 units on the PSC T3E.

BTA UNIT: T, D

TITLE: VMD: High Performance, Low Cost Molecular Visualization

KEYWORDS: molecular visualization, interactive simulation

AXIS I: 9

AXIS II: 42, 89

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% BRTP $: 12%

ABSTRACT: VMD [42] 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 new platforms, improvements to interactive molecular dynamics [43], beginning integration of bioinformatics features, increased web interaction, collaboration features, and increasing overall performance with emphasis on scalable algorithms for analysis and visualization of large molecules *. Three versions of VMD have been released in the past year, with with more than 2,000 unique registered users of the two mature releases. Approximately 15% of registered users are NIH funded researchers.

Many new features and improvements have been implemented in VMD in the past year. VMD now includes support for Python for high performance, object-oriented scripting. Tcl scripting performance has been improved, with many commands running 30 to 200 times faster. VMD now provides sophisticated rendering controls over lighting, shading, color and transparency. Other advancements include a factor of three speed increase when rendering lines and solid surfaces, wireframe surface display, and anaglyph stereoscopic rendering. New file readers provide support for Gromos format structure and trajectory files. VMD now provides new user interfaces including a new "Mouse" form for atom picking, a new "RMSD fit"

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

interface, sequence browsing and structure highlighting, collaborative visualization features, and support for the "TkCon" Tcl development console. VMD has also been ported to Mac OS X, Alpha and PowerPC versions of Linux, and 64-bit versions of IRIX and Solaris.

Future VMD development will focus on enhancing user friendliness, further work in integrating bioinformatics features into VMD, extensive BioCoRE and web-enablement features, easier methods for creating animations and movies of molecular simulations, and significant improvements to publication-quality rendering capabilities.

BTA UNIT: T, D

TITLE: Molecular Dynamics Software Modularization

KEYWORDS: molecular dynamics simulation, software design, software modularization

AXIS I: 9

AXIS II: 42

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% BRTP $: 1%

ABSTRACT: Work has been undertaken to make MD software truly modular by separating programs into a front end and computational engine. The engine includes all of the code that performs the numerical computation for each timestep of an MD simulation. The front end contains everything else that is needed for performing an MD simulation, including the setup of the simulation, the analysis of results, and all I/O. Separating an MD program allows a user-friendly front end supporting a variety of file formats to be developed independently from an optimized computational engine without concern for introducing side effects into the numerical portions of the program. To achieve this separation, a well-defined interface, the MDAPI* (molecular dynamics application programming interface), has been developed and documented.

The third generation of NAMD will incorporate the MDAPI in order to improve NAMD's modularity. The MDAPI also benefits other projects by allowing front ends to interoperate with computational engines. Special purpose engines can be interfaced to an existing front end, eliminating the need to re-create much of the program code required for an MD simulation. The MDAPI also hides a communication layer that enables the front end and computational engine to run on different machines connected by a network. A single front end can control multiple engines, allowing much improved implementations of some non-traditional techniques such as the full multiple spawning method, a QM procedure that uses many MD trajectories simultaneously to explore multiple electronic states [86, 87]. Presently, the MDAPI has been demonstrated to work by interfacing a simple front end and I/O

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

library to an engine that performs basic dynamics. The external release of this software along with the MDAPI documentation is planned for June 2001. The existing engine will also serve as a vehicle for algorithm testing and development.

BTA UNIT: T

TITLE: Multiple Grid Methods for Electrostatics

KEYWORDS: fast electrostatic methods, hierarchical interpolation

AXIS I: 9

AXIS II: 42

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% BRTP $: 1%

ABSTRACT: NAMD can utilize the fast multipole algorithm implemented in DPMTA [88] for the calculation of electrostatic forces for nonperiodic systems. This is a great improvement over the direct calculation but remains the bottleneck for performance. An alternative approach, the multigrid method, based on a hierarchical interpolation of softened pairwise potentials on multiple grids has been explored.* Like the fast multipole algorithm, this method scales linearly with the number of particles and scales well to large numbers of processors. Very limited testing indicates that the multigrid method runs twice as fast as DPMTA for the same accuracy. Also, it generalizes easily to other potentials such as van der Waals. The advantages of the multigrid method are expected to be even greater when used with dynamics. With the multigrid method it is easy to interpolate the potential so that it is continuously differentiable, permitting stable energy-conserving dynamics for even less accurate approximations. The multigrid method automatically performs a continuously varying separation of the potential into different length scales which can be exploited by multiple time stepping in order to reduce the frequency of communicating intensive long-range forces on a parallel computer. Future plans involve testing the multigrid method with dynamics and extending the method to periodic systems.

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

BioCoRE: A Collaboratory For Structural Biology* – Supplement Award

BTA UNIT: T, C, D
% BRTP $: 22%

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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

Substantial progress has been made on the BioCoRE project in the past year. We have released a number of exciting new BioCoRE components to the public.

The job submission and monitoring tool has been rewritten using Java Servlets and a small Java applet (the previous version was written entirely as a Java applet). This has allowed us to greatly expand the usefulness of the tool and it can now be used to submit any generic computational job to various supercomputers (currently the Pittsburgh

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

Supercomputer Center's T3E, NCSA's Origin 2000, and the Resource's various computational machines). User's of this tool can have simulations running at all of these sites and view their current status by going to a single webpage from within BioCoRE. If the user is running a NAMD[†] simulation additional information is also given to the user, primarily in the form of a Java applet that provides graphs of key data as well as images of the molecule that are produced by VMD[‡].

Last fall, the BioCoRE team released a BioCoRE Control Panel Java applet that has been quite popular. The applet appears as a small box in the lower left corner of the user's desktop and provides the user with real-time information about their interactions with BioCoRE. The Control Panel can be used for real-time text-based chatting on a project-by-project basis. In addition, other useful information is sent to the Control Panel such as notification when users log in and out of BioCoRE and notification when users post new messages to the Message Board.

BioCoRE has also released a NAMD configuration file generator. This tool, which is a Java applet, gives users a pleasant graphical interface where they can create or modify a NAMD configuration file. The tool has NAMD logic built in which allows it to verify that the user is creating their configuration file in a syntactically correct manner.

BioCoRE's interaction with VMD has been enhanced over the past year. Now, it is possible for researchers to actually "save" a particular view in VMD to the BioCoRE notebook. Once this is saved that user (or any other user in the same project) can instruct BioCoRE to start VMD and load this view.

BioCoRE now has a website link library that is available for its users. This is, essentially, a project-wide bookmark file that all members of a given BioCoRE project can access from any web browser. Users can add links and edit links that they have added and others can automatically see the additions. If the user chooses, other users in the project can be notified via their Control Panel that the link library has changed.

BioCoRE has also obtained official secure webserver certificates which allow users to easily connect via SSL/https and we were also the first group on campus to request and obtain an official secure developer's certificate, which allows us to "sign" our Java applets so that users can easily give the applets permission to do certain things (such as access files on the user's computer). We have also upgraded versions of most of the software that we use so that we can stay on the cutting edge of technology.

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

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

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 decide to use BioCoRE 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. The user gives their email address, which is used to email them a temporary password. The user then can log into BioCoRE using this password and change to something that only they know. After this first-time registration users can use their username/password combination to gain regular access to BioCoRE.

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 benefiting from new additions to the collaboratory. As of April 13, 2001, 224 researchers have registered to use BioCoRE, collaborating on projects involving biophysics training, joint document preparation, and molecular functions.

The BioCoRE team is actively working on preparing the Java servlet codebase for release to other research groups that wish to run their own local BioCoRE server. We have installed a "remote" local server in Todd Martinez' research group and are using it to debug any possible problems that we have with additional local servers. As soon as we are comfortable with the robustness of their local server will make it possible for any research group to download and install a local BioCoRE server.

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

[§]Email Address: `biocore@ks.uiuc.edu`

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 evaluation program is to provide user information to developers for further refinement of the collaboratory environment. Over the past year the evaluation team has continued to assist the BiocoRE development by anchoring the development efforts in a relevant context representing the typical working environment of structural biologists. The team further studied scientists' work habits and provided better need analysis to the development team. The evaluation activities also included usability tests on BioCoRE components, reliability and validity analyses of BioCoRE scales designed to measure self efficacy and satisfaction in BioCoRE users, and the design and administration of user surveys to evaluate in-house software products that are about to be incorporated into BioCoRE.[¶]

To provide more in-depth data on work habits, recent efforts encompassed intensive interviews with Resource members focusing on time management during collaborative projects and their preferences concerning the BioCoRE Workbench, Notebook, Conferences, and Documents components [‖] The interviews' data were used to develop a functional analysis of scientist work behaviors during collaborative projects. Drawn from the fields of industrial/personnel psychology and job analysis, a functional analysis describes work behavior in terms of tasks, functions within a task, and smaller unit behaviors within functions. The functional analysis of scientist work behavior thus provides BioCoRE developers with a detailed look at tasks common to scientific collaborative work. Additionally, to improve the BioCoRE registration form and improve the definition of users' disciplinary affiliation, a card-sort procedure of fields of study listed by BioCoRE registrants was conducted with six users.

As they are developed, BioCoRE components are subjected to usability testing to provide developers with information about user needs and preferences. Initially, the developers and evaluation teams conduct a usability analysis of components before they are released; then the components are put before users for further evaluation. Recent usability testing subjects were the BioCoRE Control Panel and the NAMD Configuration File Generator (NAMD-CFG), a tool for generating NAMD input files. Developers first used paper-based, iterative rapid-prototyping to refine the BioCoRE Control Panel; scientist input was then gathered using a cognitive-walk through of the new component. Heuristic

[¶] http://www.ks.uiuc.edu/Research/biocore/scales/BioCoRE_SATCO_Scale_Report.pdf

[‖] http://www.ks.uiuc.edu/Research/biocore/interview.shtml

analysis was used first by the development team, and then scientists/users, to evaluate the NAMD-CFG.

The BioCoRE plan also mandates that the evaluation team develop new measures to apply to the collaboratory environment. Two measures developed for BioCoRE, the Collaboration Technology Self-Efficacy Scale (CTSE)** and the Satisfaction with Collaboration Scale (SATCO)†† , were assessed for reliability and validity using registration data from March to November 2000. Results indicated satisfactory reliability for the CTSE, but suggested revision for the SATCO. A revised version of the SATCO was placed on the BioCoRE registration form at the end of November 2000.

The BioCoRE evaluation team has also assisted in the evaluation of VMD and NAMD user data. Specifically, the BioCoRE evaluation team provided statistical analysis and interpretation of the VMD 2000 Survey* and NAMD 2000 Survey† data sets. The two programs are the first to be launched from within BioCoRE.

Tools to access BioCoRE user data have been developed over the last year including a web-based tool to access the BioCoRE event database, through pre-set scripts or through custom SQL scripts. Statistics describing BioCoRE databases are also described on a web page that is updated nightly; login statistics, message board and chat channel changes, are just a few of the statistics shown by this page. A feedback form is posted on the BioCoRE front page with real-time tallying of results.

The evaluation team has been grappling with the need to identify an appropriate theoretical architecture to frame the evaluation program. Theory applied to groupware typically emphasizes a single topic (e.g. communication channels or a particular feature [89]) or has been an ill fit due to assumptions about the state or context of a product (e.g. adaptive structuration and diffusion of innovations product [90, 91]). The best option for the BioCoRE evaluation program appears to be a fusion of two acknowledged models used for technology evaluation: the Triandis model of the antecedents of action [92, 93] and the Technology Acceptance Model (TAM) [94, 95]. The Triandis model is more comprehensive in identifying factors that influence technology acceptance, but lacks specificity in identifying perceived software attributes. The TAM lacks scope, but is more specific in identifying perceptions of software. When combined, the two models promise to provide a theoretical architecture to frame BioCoRE evaluation research, and to explain overall patterns of BioCoRE use by scientists.

**http://www.ks.uiuc.edu/Research/biocore/scales/BioCoRE_CTSE_Scale_Report.pdf

††http://www.ks.uiuc.edu/Research/biocore/scales/BioCoRE_SATCO_Scale_Report.pdf

*http://www.ks.uiuc.edu/Research/vmd/survey/report2000/vmdsurvey2000rep.pdf

†http://www.ks.uiuc.edu/Research/namd/survey/NAMD2000_results.pdf

Other evaluation work for the next year includes usability assessments of the newly released BioCoRE Job Submission Tool and Shared VMD Tool, and prototyping of the file storage/database component of the BioCoRE environment. Where needed, more inquiry into scientists work habits will occur, such as interviews to help supplement the functional analysis description of file systems used by scientists. Reports summarizing the body of interview data, BioCoRE registrant data and users profile, and the theoretical architecture of the BioCoRE evaluation program will be completed in the immediate future. The greatest challenges for the evaluation team over the next year will be developing meaningful indicators of the unobtrusive data found in the BioCoRE database structure, and studying the use of analogy within scientific discussions found within BioCoRE.

Personnel

Presently the Resource has four 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.

New Hardware

The Resource has acquired two new Sun desktop workstations (Sun Blade 100's) for use on two of the programmer's desks. In addition, we have installed a third Sun Blade in Todd Martinez' group for use as the test "remote" local BioCoRE server. We have also acquired another dual processor Sun E250 with four 73 gigabyte disks to serve as a file server for the collaboratory.

Dissemination

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

The Resource has given on-site private demonstrations to both on campus researchers, such as Bruce Loftis, Sudhakar Pamidighantam (NCSA) as well as to off-campus visitors (including Olaf Kuebler, President, ETH Zurich; Ernest Retzel, Director of the Computational Biology Center U Minnesota; Rick Niles, Thomas Quinn, Scyld Computing Corporation). Resource members have also given public talks and demonstrations including the Beckman Institute Open House[‡], and the NCRR Biomedical Collaboratories Workshop [§].

[‡]URL: `http://www.ks.uiuc.edu/Research/biocore/presentations/COEOpenHouse2001/`

[§]URL: `http://www.ks.uiuc.edu/Research/biocore/presentations/NCRR_2000/`

The BioCoRE website has enjoyed significant traffic over the past year. From April 2000 - March 2001 the Resource had 37,550 accesses to the BioCoRE webpages from non-Resource machines which is an average of 103 accesses per day.

Key plans for the next 12 months

Over the next twelve months the BioCoRE team plans to increase support for 3rd party programs, implement a filesystem that can automatically move users files to and from computational machines, investigate alternative platform support for BioCoRE (such as palmtop computing), and rigorously court new users.

	TECH RES & DEVEL (T)	COLLAB RES & SERVICE (C)	DISSEM & TRAINING (D)	TOTALS
NUMBER OF PUBLICATIONS	27	9	1	37
NUMBER OF SUBPROJECTS	18	13	6	26*
NUMBER OF INVESTIGATORS	33	31	9	55*
PERCENT OF BRTP FUNDS ALLOCATED	46.5%	27%	26.5%	100%†
SERVICE FEES COLLECTED	0	0	0	0
OTHER FUNDS ($)	275,000	42,000	—	317,000

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

† Percentages may include membership in multiple categories.

State or Country	Number of Investigators
IL	31
WA	1
CA	4
MO	1
MN	1
WI	1
TX	2
France	1
Germany	1
Israel	1
Japan	1
Italy	1
UK	1
Denmark	1

BRTP Unit T

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Bach, Michael	University of Illinois (Schulten, Klaus)	FED	NIH
Balabin, Ilya	University of Illinois (Schulten, Klaus)	FED	NIH
Balaeff, Alexander	University of Illinois (Schulten, Klaus)	FED	NIH
Ben-Nun, Michal	University of Illinois (Martinez, Todd)	FED	NIH
Brandon, David	University of Illinois (Budescu, Gila)	FED	NIH
Brunner, Robert	University of Illinois (Kale, Laximkant)	FED	NIH
Damjanovic, Ana	University of Illinois (Schulten, Klaus)	OTH	
DeSouza, Jayant	University of Illinois (Kale, Laximkant)	FED	NIH
Fillingame, Robert	University of Wisconsin, Madison (Fillingame, Robert)	OTH	
Goode, Andrew	University of Illinois (Martinez, Todd)	OTH	
Gullingsrud, Justin	University of Illinois (Schulten, Klaus)	FED	NIH
Hardy, David	University of Illinois (Skeel, Robert)	OTH	
Hayashi, Shigehiko	University of Illinois (Schulten, Klaus)	OTH	
Israelewitz, Barry	University of Illinois (Schulten, Klaus)	FED	NIH
Kandori, Hideko	Kyoto University, Japan (Kandori, Hideko)	OTH	

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Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Kosztin, Ioan	University of Illinois (Schulten, Klaus)	OTH/FED	NIH NSF
Kumar, Sameer	University of Illinois (Kale, Laximkant)	FED	NIH
Mahadevan. L	Cambridge Univ., UK (Mahadevan. L)	OTH	
Manohar, Leslie	University of Illinois (Martinez, Todd)	OTH	
Morales, Jorge	University of Illinois (Martinez, Todd)	OTH	
Olivucci, Massimo	Univeersity of Sienna, Siena, Italy (Olivucci, Massimo)	OTH	
Olsen, Seth	University of Illinois (Martinez, Todd)	OTH	
Park, Sanghyun	University of Illinois (Schulten, Klaus)	FED	NIH
Phillips, James	University of Illinois (Schulten, Klaus)	FED	NIH
Ritz, Thorsten	University of Illinois (Schulten, Klaus)	OTH	
Sener Melih	University of Illinois (Schulten, Klaus)	FED	NIH
Sheves, Mordechai	Weizmann Institute, Rehovot, Israel (Sheves, Mordechai)	OTH	
Stone, John	University of Illinois (Schulten, Klaus)	FED	NIH
Suhai, Sandor	German Cancer Res. Inst., Heidelberg (Suhai, Sandor)	OTH	
Tajkhorshid, Emadeddin	University of Illinois (Schulten, Klaus)	FED	NIH
Tezcan Ismail	University of Illinois (Schulten, Klaus)	OTH	
Unger, Joshua	University of Illinois (Kale, Laximkant)	FED	NIH
Vandivort, Kirby	University of Illinois	FED	NIH

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Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
	(Schulten, Klaus)		
Wang, Hui	University of Illinois (Schulten, Klaus)	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
Bach, Michael	University of Illinois (Schulten, Klaus)	FED	NIH
Balabin, Ilya	University of Illinois (Schulten, Klaus)	FED	NIH
Brandon, David	University of Illinois (Budescu, Gila)	FED	NIH
Braun, Rosemary	University of Illinois (Schulten, Klaus)	OTH	
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
Fernandez, Julio	Mayo Clinic (Fernandez, Julio)	FED	NIH
Fillingame, Robert	University of Wisconsin, Madison (Fillingame, Robert)	OTH	
Gao, Mu	University of Illinois (Schulten, Klaus)	OTH	
Gullingsrud, Justin	University of Illinois (Schulten, Klaus)	FED	NIH
Hayashi, Shigehiko	University of Illinois (Schulten, Klaus)	OTH	
Isralewitz, Barry	University of Illinois (Schulten, Klaus)	FED	NIH
Jensen, Morten	Technical University of Denmark (Schulten, Klaus)	OTH	
Kandori, Hideko	Kyoto University, Japan (Kandori, Hideko)	OTH	

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Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Kosztin, Ioan	University of Illinois (Schulten, Klaus)	OTH/FED	NIH NSF
Kumar, Sameer	University of Illinois (Kale, Laximkant)	FED	NIH
Landau, Ehud M.	University of Texas Medical Branch (Landau, Ehud M.)	OTH	
Lu, Hui	Danforth Plant Science Center (Skolnick, Jeff)	OTH	
Mitra, Alok K.	The Scripps Research Institute (Mitra, Alok K.)	OTH	
O'Lague, Paul	UCLA, CA (O'Lague, Paul)	OTH	
Olivucci, Massimo	Univeersity of Sienna, Siena, Italy (Olivucci, Massimo)	OTH	
Pebay-Peyroula, Eva	Université Joseph Fourier, France (Pebay-Peyroula, Eva)	OTH	
Sarikaya, Mehmet	University of Washington, Seattle (Sarikaya, Mehmet)	FED	NIH/NSF
Sheves, Mordechai	Weizmann Institute, Rehovot, Israel (Sheves, Mordechai)	OTH	
Skirvin, Tim	University of Illinois (Schulten, Klaus)	FED	NIH
Stroud, Robert	University of California, San Francisco (Stroud, Robert)	OTH	
Suhai, Sandor	German Cancer Res. Inst., Heidelberg (Suhai, Sandor)	OTH	
Tajkhorshid, Emadeddin	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
Zhu, Fangqiang	University of Illinois (Schulten, Klaus)	OTH	

BRTP Unit D

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Bach, Michael	University of Illinois (Schulten, Klaus)	FED	NIH
Brandon, David	University of Illinois (Budescu, Gila)	FED	NIH
Brunner, Robert	University of Illinois (Kale, 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	
Kumar, Sameer	University of Illinois (Kale, Laximkant)	FED	NIH
Phillips, James	University of Illinois (Schulten, Klaus)	FED	NIH
Skirvin, Tim	University of Illinois (Schulten, Klaus)	FED	NIH
Stone, John	University of Illinois (Schulten, Klaus)	FED	NIH
Unger, Joshua	University of Illinois (Kale, Laximkant)	FED	NIH
Vandivort, Kirby	University of Illinois (Schulten, Klaus)	FED	NIH
Wang, Hui	University of Illinois (Schulten, Klaus)	FED	NIH
Zheng, Gengbin	University of Illinois (Kale, Laximkant)	FED	NIH

BTA unit: (T)

NUMBER PUBLISHED –
Books: 0 Papers: 17 Abstracts: 0

NUMBER IN PRESS OR SUBMITTED –
Books: 0 Papers: 10 Abstracts: 0

Books:
None

Papers
Published: 17

1. M. Ben-Nun, J. Quenneville, and T. J. Martínez, "Ab Initio Multiple Spawning: Photochemistry from First Principles Quantum Molecular Dynamics," *J. Phys. Chem.* Invited Feature Article, 104, 5161 (2000).

2. M. Ben-Nun and T. J. Martínez, "Direct Observation of Disrotatory Ring-Opening in Photoexcited Cyclobutene Using Ab Initio Molecular Dynamics," communication to *J. Amer. Chem. Soc.,* 122, 6299 (2000).

3. M. Ben-Nun and T. J. Martínez, "A Multiple Spawning Approach to Tunneling Dynamics," *J. Chem. Phys.,* 112, 6113 (2000).

4. M. Ben-Nun and T. J. Martínez, "Photodynamics of Ethylene: Ab Initio Studies of Conical Intersections," *Chemical Physics*, 259, 237 (2000).

5. A. Damjanovic, T. Ritz, and K. Schulten, "Excitation transfer in the peridinin-chlorophyll-protein of Amphidinium carterae." *Biophysical Journal*, 79:1695-1705, 2000.

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7. J. Gullingsrud, D. Kosztin, and K. Schulten, "Structural determinants of MscL gating studied by molecular dynamics simulations." *Biophysical Journal*, 80:2074-2081, 2001.

8. J.A. Izaguirre, D.P. Catarello, J.M. Wozniak, and R.D. Skeel, "Langevin stabilization of molecular dynamics." *J. Chem. Phys.* 114, 2001, 2090–2098.

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10. H. Lu and K. Schulten, "The key event in force-induced unfolding of titin's immunoglobulin domains." *Biophysical Journal,* 79:51-65, 2000.

11. F. Molnar, M. Ben-Nun, T. J. Martínez, and K. Schulten, "Characterization of a conical intersection between the ground and first excited state for a retinal analog." *Journal of Molecular Structure* (THEOCHEM), WATOC special issue, 506:169-178, 2000.

12. D. B. Moore and T. J. Martínez, "Ab Initio Study of Coupled Electron Transfer/Proton Transfer in Cytochrome c Oxidase," invited article for W. A. Goddard III Festschrift, *J. Phys. Chem.*, 104, 2367 (2000).

13. T. Ritz and K. Schulten, "Physik der Photosynthese." *Physikalische Blaetter*, 57:49-53, 2001.

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2. R. Brunner and J. Phillips and L. V. Kale, "Scalable Molecular Dynamics for Large Biomolecular Systems," (Finalist for Gordon Bell Award) *Proceedings of SC2000* CD-*ROM*, Dallas, In press, Nov 2000.

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4. J. Quenneville, M. Ben-Nun, and Todd J. Martínez, "Photochemistry from First Principles: Advances and Future Prospects," *J. Photochem. Photobiol.*, In press, 2001.

5. T. Ritz, S. Park, and K. Schulten, "Kinetics of Excitation Migration and Trapping in the Photosynthetic Unit of Purple Bacteria", *Journal of Physical Chemistry B,* Submitted, 2001.

6. I. Kosztin, R. Bruinsma, P. O'Lague and K. Schulten, "Mechanical Force Generation by G-proteins", *PNAS,* Submitted, 2001.

7. A. Damjanović, I. Kosztin, and K. Schulten, "Absorption spectrum and delocalization length of excitons in light-harvesting complex II of *Rhodospirillum molischianum*: a combined molecular dynamics/quantum chemistry and quantum dynamics study", *Physical Review E*, Submitted, 2001.

8. M. Sener and K. Schulten, "Spectral Properties of the Light-Harvesting Complexes of Purple Bacteria", *Physical Review E*, Submitted, 2001.

9. Saboo, N., Signla, A., Unger, J., and Kale, L.V., "An emulator for blue gene class machines", In *Proceedings of the workshop on massively parallel computing, IPDPS-2001*, San Francisco, CA, In press, April 2001.

10. R.D. Skeel and D.J. Hardy, "Practical construction of modified Hamiltonians," Submitted, 2001.

Abstracts:
None

BTA unit: (C)

NUMBER PUBLISHED –
Books: 0 Papers: 7 Abstracts: 0

NUMBER IN PRESS OR SUBMITTED –
Books: 0 Papers: 2 Abstracts: 0

Books:
None

Papers
Published: 7

1. J. Baudry, E. Tajkhorshid, F. Molnar, J. Phillips, and K. Schulten. "Molecular dynamics study of bacteriorhodopsin and the purple membrane." *Journal of Physical Chemistry B*, 105:905-918, 2001.

2. D. Craig, A. Krammer, K. Schulten, and V. Vogel. "Comparison of the early stages of forced unfolding of fibronectin type III modules." *Proceedings of the National Academy of Science*, USA, 98:5590-5595, 2001.

3. B. Isralewitz, M. Gao, and K. Schulten, "Steered molecular dynamics and mechanical functions of proteins". *Current Opinion in Structural Biology*, 11:224-230, 2001.

4. A. Kessel, K. Schulten, and N. Ben-Tal. "Calculations suggest a pathway for the transverse diffusion of a hydrophobic peptide across a lipid bilayer." *Biophysical Journal*, 79:2322-2330, 2000.

5. 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, pages 143-162. Kluwer Academic/Plenum Publishers, New York, NY, 2000.

6. F. Molnar, L. S. Norris, and K. Schulten. "Simulated unbinding and binding of fatty acid substrates in the cyclooxygenase site of prostaglandin H2 synthase-1." *Progress in Reaction Kinetics and Mechanisms,* 25:263-298, 2000.

7. T. Ritz, A. Damjanovic, K. Schulten, J-P. Zhang, and Y. Koyama. "Efficient light harvesting through carotenoids." *Photosynthesis Research,* 66:125-144, 2000.

Submitted or In Press: 2

1. S. Hayashi, E. Tajkhorshid, E. Pebay-Peyroula, A. Royant, E. M. Landau, J. Navarro, and K. Schulten. "Structural Determinants of Spectral Tuning in the RhodopsinFamily of Proteins." *Journal of Physical Chemistry B,* Submitted 200l.

2. T. W. Lynch, D. Kosztin, M. A. McLean, K. Schulten, and S. G. Sligar. "Dissecting the Molecular Origins of Protein-Nucleic Acid Recognition: High Pressure and Molecular Dynamics" *Biophysical Journal,* Submitted 2001.

Abstracts:

None

BTA unit: (D)

NUMBER PUBLISHED –
Books: 0 Papers: 1 Abstracts: 0

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

Books:
None

Papers:

1. Klaus Schulten. "To students contemplating research in biomolecular modelling." *Journal of Molecular Graphics and Modeling*, 18:218-220, 2000.

Abstracts:
None

Web Documents:

Advisory Committee

The Resource Advisory Board met on May 2, 2001, and produced the following report (see appendix A for the agenda):

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

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

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

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

The program NAMD is an object-oriented molecular dynamics parallel code designed for high-performance simulations of large biomolecular systems. It is distributed free of charge and includes source code. It has two main advantages: the very high scalability in parallelization (hundreds of CPUs), and the modularity of the source code (written

in C++). The first advantage is important because the availability of large number of relatively inexpensive computers is expected to increase. The second advantage is also very important since it allows potential users and collaborators to implement new computational methodologies in the code without disrupting the structure of the program. Despite the impressive performance of NAMD, it appears to be very difficult to spread its usage throughout the scientific community (which remains dominated by AMBR, CHARMM, and GROMOS). It might be a good idea to organize additional practical workshops to decrease the barriers for using a new program.

Turning to steered molecular dynamics, several projects are under investigation; all are of outstanding scientific interest and executed at the highest level of competence.- Unfolding of Titin; Excellent integration of experimental results(mechanical unfolding by FM) and simulation. Good example of cross-fertilization between experimentalists and modelers. - Mechanosensitive channels; surface tension is applied in the simulation and results in tilting of the helices with concomitant expansion of the protein structure. An expansion of the channel has been suggested from experimental results.- ATP synthase; this is an excellent example of a molecular machine. The simulation in this case is a steered MD simulation using torque. Observations from the simulation results can help explain the mechanism of the machine.

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

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

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

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

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

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

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

Organization, Service, Training and Dissemination

I. Resource Organization

Our R&D core activities are translated into operational terms that could all be classified into two general areas: development work to create research tools and methods, and collaborations that use the tools to promote research. Both these activity areas have vast potential and practical implications for the Resource and the biomedical community at large. Through service, training and dissemination we transfer the outcomes and deliver the technologies to the environment and to specific target groups such as scientists at other universities and research institutions, government and industrial organizations, etc.

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

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

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

These three forces and other factors have infused renewed energy and urgency to our activities and are reshaping our scope and practices daily. The size of the Resource is unprecedented – over 40 members (graduate assistants, postdoctoral associates, developers, faculty, administrative and technical staff); the number and size of systems modeled here are un-matched; our computational resources are much bigger than ever before and are effectively utilized.

Organization-wise our visibility thanks to the web has expanded many-times over, and with that, the service, training and dissemination opportunities, and the complexity of our relationship with our environment have tremendously widened.

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

We value, and very early on adopted, the extensive use of the web for management and information sharing, as well as other technologies like databases and such. Just like our approach toward cluster computing we always seek to take advantage of any proven and creative cost-effective solutions that we think would improve administration and yet, would cost less and be simple to integrate.

Computational Facility

We have experienced significant increase in local power in the past funding period and with every new cluster we purchase we get more power for less.

We enjoy the respect and great cooperation of the NSF supercomputer centers and in the past year our time allocations have more than doubled compared to the year before. This welcome generosity reflects obviously more resources on the national level and highlights the importance of our research efforts.

Our local platforms include

1. Three 32-node Linux clusters
2. Four dual-processor Alphas
3. One 8-processor Onyx2

Our local computer resources have substantially increased in the past year: about 78% in computational power and about 233% in disk space. Both power and space are critical for successfully performing the huge and demanding simulations our members perform. The third cluster has brought a 211% increase compared to last year.

Our external platforms are

1. PSC T3E (300,000 SU)
2. NCSA Origin 2000 (178,000 SU)
3. PSC TCS1 (69,498 SU)

Our external resources have increased this year by 139%.

Regarding our graphics capabilities, only a couple of years ago our members had to use 4 public SGIs, about $30K each, to do their graphics work. Today each of our researchers has a graphics desktop for a fraction of the cost of the old SGI machines. Moreover, some of these desktops are 'recycled' old cluster boxes (our 1st PC cluster) that with a low-cost card were converted into a graphics resource rather than surplussed after dissembling that cluster.

Key Improvements in 2000-01

Our key administrative improvement

1. Publications – all Resource publications are now stored in a database
2. Online Library – the Resource library relies on a database
3. Hardware/Software Database allows for better documentation and accountability
4. System Loads – through the use of a database we can simply and quickly monitor the usage pattern of our computational resources in real time
5. Address Book – storing all contact information of colleagues, vendors, government agencies, etc. in a web-based database helps in daily communications, in service and dissemination efforts, in collaborations and more

These effectiveness-enhancing instruments have taken advantage of our own web-based database development and resulted in benefits that cut across daily administration, sysadministration support, research, dissemination, etc. This is only a sample of our various database uses. Another major use is our extensive software user database in which all of our software downloads are documented with data pertaining to standard details such as ID information and the platform the software is to be used on, as well as what the software will be used for and other agency-relevant information such as source of funding (NIH or other), affiliation (government, academia, etc). That kind of data we often need for reporting purposes and in response to NIH inquiries. This particular database is extremely instrumental for software evaluation purposes which will be discussed later.

II. Service, Training and Dissemination

The web is by clear choice our key management, service, training and dissemination tool. In the past year we had redesigned the Resource web site and adopted a more contemporary look while at the same time adding functionality, keeping the simplicity and enriching content and substance. Two of the new features on our front page are

1. The highlight section, which makes our front page more relevant and anchored in the right context. The highlight, in an immediate and effective fashion, illuminates the page and the entire site in the right light. Moving forward to the Previous Highlights section offers the visitor our latest published examples of the Resource work and some sense of overview. This section has also a very practical function – we are often asked to provide highlights to various agencies and centers on and off campus and here we have relevant and up-to-date highlights both furnishing our site with substance which is also ready-to-use for other purposes.

2. New publication section relies on our publication database that stores data on our entire publication process, from the very first submission through the proof stage and reprints distribution. The database allows the Resource to document each and every publication-related action, share the full information with the other co-authors, and make the papers once out in press, available in abstract and full pdf off our web site. It took us months of concerted efforts to document and formulate the entire process, in order to develop a well-designed database that would satisfy each and every aspect of this complex system, to locate reasonably-looking full text documents of our old as well as new papers, get the necessary permissions, and scan/post them onto the web with close attention to copyright laws that govern distribution. The search function facilitated by the database is obviously another friendly feature turning our publication section into an easily accessible library. All in all, like with the rest of the site, here too we have been seeking functionality, form and content with a special emphasis on simplicity.

At present the process works flawlessly and all new submissions end up on the web as soon as they are accepted for publication. This helped us with the actual publication process, made it so much easier for others to get access to our published work, and consequently has greatly widened the distribution and impact of our work.

Service

1. Software

All the programs are available on our web-site for easy accessibility employing, where needed, the same simple yet sophisticated distribution mechanism we have already had in place for the lead programs. Some require more and some less effort to develop and maintain. They have been contributed and maintained by developers and researchers and once they are on our site the same professional criteria of quality, support, etc, that apply to NAMD, VMD and BioCoRE apply to them . Statistics on NAMD, VMD and BioCoRE, our flagship programs, will be presented in the next section. Here we would like to give a picture of our overall software offering which have dramatically increased in the past year.

- NAMD
- VMD
- BioCoRE

- JMV
- MDTools
- MDSalon
- BioSoft DB

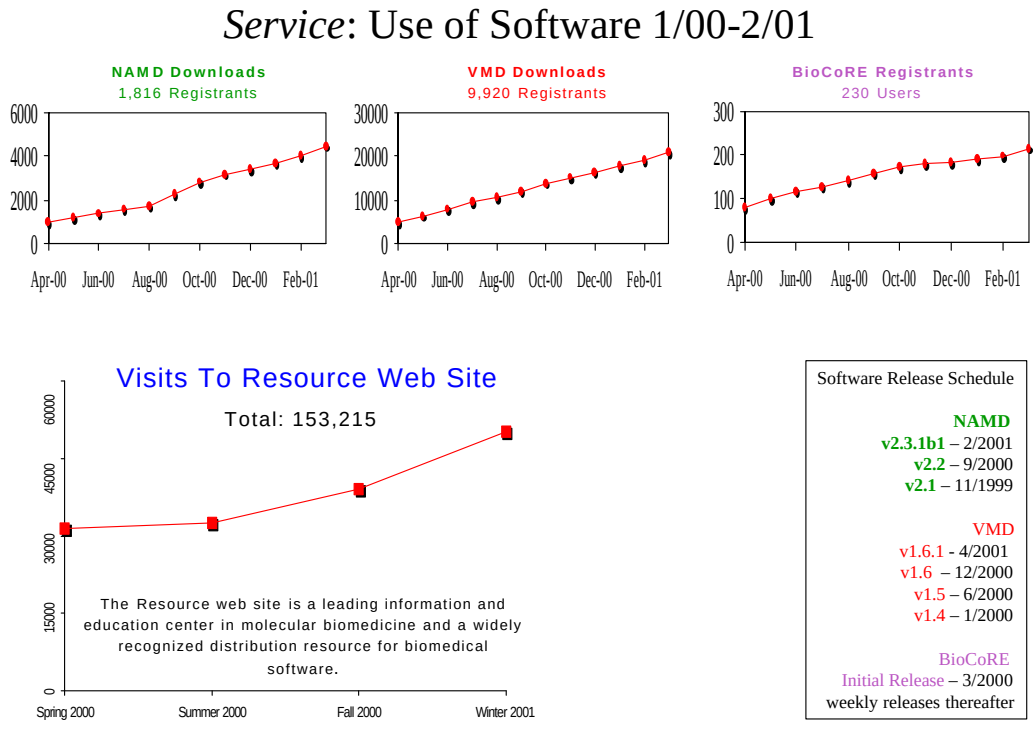
JMV – JMV is a molecular viewer written in Java and Java3D. JMV is designed to be an easy-to-use, platform neutral, molecular visualization tool, which can be used standalone, or integrated into a larger program.

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

MDSalon – MDSalon offers a friendly (web) location for molecular dynamics practitioners and developers to exchange ideas.

BioSoft DB – This database was opened to the public in 1/2001 and already contains close to 300 programs which are of interest to researchers in the fields of structural biology, quantum chemistry, and bioinformatics. As of last week it had about 3,500 unique visits!

2. Use of Software 2000-01



Between April 2000 and May 2001 the number of VMD registrants reached 9,920, and the number of VMD downloads went up from 3,500 to over 20,000. In a similar fashion, the

number of NAMD registrants went up to 1,816, and the number of NAMD downloads went up from 800 to over 4,000. During that same period, the number of BioCoRE registrants went up to 233 since its initial release a year ago.

The improved appeal and usability of the Resource web site has led to consistently growing numbers of unique visits, with each quarter in the past year posting a significant increase of visitors. Between Fall 2000 and Winter 2001 there was an increase of more than 15,000 unique visits to our site. The total number of unique visits to the Resource web site in the past funding period is 153,215.

The software release schedule of the Resource's lead programs boasts great productivity and lively activity with several releases a year for VMD and NAMD, and following its initial release, weekly releases of BioCoRE updates.

NAMD was included in the newly released Scyld CD bringing NAMD to a much larger and heterogeneous population of users.

3. Key improvements in the past year

NAMD

- NAMD 2.2
  - New ports to the IBM RS/6000 SP, Alpha Linux, and Windows.
  - Parallelized particle mesh Ewald FFT and reciprocal space sum with demonstrated scaling to 128 processors for large systems.
  - Release binaries contain FFTW (under special license) for better serial performance when using particle mesh Ewald.
  - Much faster minimizer based on conjugate gradient method, also more stable when dealing with very bad initial contacts.
  - Improved load balancer with demonstrated scaling to over 1024 processors for large cutoff systems.
- NAMD 2.3
  - The new psfgen tool for building PSF structure files.
  - Simpler to run on a single workstation. (No more rsh!)
  - New ports to the Compaq AlphaServer SC, Scyld Beowulf, VMI Linux clusters, Mac OS X, Windows/IA64 and Linux/IA64.

  - Up to 50% faster serial performance due to improvements to particle mesh Ewald direct space

- New platforms and where
  - IBM RS/6000 SP (SDSC Blue Horizon)
  - Compaq AlphaServer SC (PSC TCS1)
  - VMI Linux clusters (NCSA POSIC and Platinum)
  - Scyld Beowulf (local cluster, distribution on Scyld CD)
  - Windows
  - Windows/IA64 (NCSA)
  - Mac OS X
  - Alpha Linux
  - Linux/IA64 (NCSA)

NAMD installations are maintained at PSC, SDSC, and NCSA.

- NAMD key features for next 12 months
  - Ability to read AMBER force field and molecule file formats.
  - Modular front-end interface using MDAPI library.
  - Ability to perform alchemical free energy perturbation calculations.
  - Improvement and extension of structure building tool.
  - Improved scaling on large terascale clusters (PSC, NCSA, SDSC).
  - Incorporation of NAMD and structure building into VMD interface.
  - Improved documentation and user education materials.

- NAMD talks (date, title, location)
  - November 8, 2000
    "Scalable Molecular Dynamics for Large Biomolecular Systems"
    SC2000, Gordon Bell Award Finalist
    Dallas, Texas
  - March 21, 2001
    "A System for Interactive Molecular Dynamics Simulation"
    ACM Siggraph 2001 Symposium on Interactive 3D Graphics
    Research Triangle Park, North Carolina

There are currently 27 external users with access to the NAMD CVS tree.

VMD

In the past year there were 712,690 hits to the VMD web pages (excluding image hits) for an average of 1953 web hits per day.

Key improvements in the past year:

- Support for the Python scripting language
- Support for Gromos and Gromacs structure and trajectory file formats
- Multithreaded communications for IMD simulations, beginnings of support for multithreading for the rest of VMD.
- BioCoRE "publish" and "sync" features
- Collaborative VMD sessions (non-BioCoRE, "VMDChat" script)
- Sequence display and highlighting ("ZoomSeq" script)
- Significant surface rendering speed improvements
- A tenfold increase in speed and responsiveness of IMD simulations
- Entirely new "material" properties which can be applied to a molecular representation giving the user much more powerful control over the way molecules are shaded and rendered in VMD.
- New wireframe surface rendering representation
- Support for stereoscopic display on machines with 12-bit color.
- New "Mouse" form which provides a more powerful picking and labeling interface which is now identical for both Unix and Windows versions of VMD.
- New feature to export VMD molecular graphics to Renderman .RIB files for use in professional animation packages.
- Line drawing performance 3 times faster
- Performance increases between 10 and 30 times faster for complex atom selections on large molecules with hundreds of thousands of atoms.
- Improved user interface responsiveness when working on large molecules

New platforms VMD now runs on

- MacOS-X (XFree86-based port)
- Linux/PowerPC
- Linux/Alpha
- 64-bit SGI IRIX 6.5.x
- 64-bit Sun Solaris 8

Number of VMD demos offered in the past year

- 65 VMD demos given at TB in last 12 months.
- 144 VMD CAVE demos given at NCSA in last 12 months.

A VMD talk was presented at

- ACM Siggraph 2001 Symposium on Interactive 3D Graphics Research Triangle Park, North Carolina, March 21st, 2001

  Title: "A System for Interactive Molecular Dynamics Simulation"

Key features for next 12 months

- Collaborative VMD sessions using BioCoRE for session management
- Implementation of further BioCoRE interfaces in VMD to provide better collaborative use of VMD.
- Support for MacOS-X with full hardware accelerated OpenGL rendering
- Further multithreading of VMD for increased performance and improved user interface responsiveness.
- Simplified mechanisms for producing animations using VMD.
- Improved molecular representations and external renderer scene exports for publication-quality rendering, and animation.
- Audio capabilities added to user interface

- Extensions and improvements to the interactive molecular dynamics features in VMD.
- New coloring methods for data which is not particularly atom-oriented
- Extension of existing sequence display and highlighting features
- Electron orbital display, extensions to existing EDM file display capabilities.
- Improved VMD state saving, with further BioCoRE integration, and potential support for file associations on Windows and MacOS.
- Support for reading and writing of compressed molecular dynamics trajectory files
- Continued VMD "scalability" improvements to allow researchers to visualize larger macromolecules
- New animation features to give researchers more control of animated atom selections.

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BioCoRE

Key accomplishments in the past funding period include

- Simulation submission at remote sites (PSC, NCSA, and Resource machines)
  - Monitor all of your jobs from one web page
  - Run any program installed on remote machine
- Additional support for NAMD

- Support for additional Molecular Dynamics programs upcoming
- BioCoRE Linux cluster
- NAMD configuration file generator
  - Context-sensitive help
  - Error prevention
- Control panel
  - Instant messenger, instant notifier
- Website library - Project-wide "bookmarks" file
- VMD Publish/Synchronize

Future plans include

- Integrated file system
  - All project files accessible from one place
- JMV applet integration
- Grid-based computing (Globus) support (NCSA)
- Tighter integration with discipline-specific applications
- Release of local servers
- Heterogeneous access (wireless, etc)
- Audio/video conferencing
- Additional training features

As of April 2000 there were 32 projects created within BioCoRE and 996 logins from 4-4-2000 to 4-10-2001.

Since BioCoRE is a purely web-based program the release mechanisms are different than with traditional programs such as VMD/NAMD. For BioCoRE itself, the user is not required to download anything. They simply access a website.

This has given us considerable flexibility in how we handle updating the BioCoRE code. We have set aside a time each week that we update the BioCoRE codebase. We use this time to release the new java servlets that we have been working on.

We have recently installed a test server in Todd Martinez' group. Once testing is complete we will allow interested users to download and install the BioCoRE server on their machines so that their group can use it locally. Even at that time, though, regular users won't have to download BioCoRE. Only system administrators will download BioCoRE. They will then install it on their computers and their users can use it simply by going to a webpage.

BioCoRE demos given in the past funding period include

May 1, 2000: HICS Conference, Beckman Institute, *Demo of BioCoRE/Haptic* (20 visitors) http://www.ks.uiuc.edu/Research/biocore/presentations/HICS_2000/

May 11, 2000: BioCoRE Demo, Beckman Institute (Olaf Kuebler, President, ETH Zurich; Thomas Eichenberger, Assistant to the President; Computer Science Professors: Moira Norrie, Peter Windmayer, Walter Gander)

July 17, 2000: BioCoRE Demo, Beckman Institute (Ernest Retzel, Director of the Computational Biology Centers, U of Minnesota)

March 2,3 2001: 2001 College of Engineering Open House, *BioCoRE Demo* (120 visitors) http://www.ks.uiuc.edu/Research/biocore/presentations/COEOpenHouse2001/

March 22, 2001: BioCoRE Demo, Beckman Institute (Scyld Computing Corporation Management)

April 6, 2001: BioCoRE Job Submission/Monitoring demo, Beckman Institute (NCSA visitors)

BioCoRE talks in the past year include

April 27, 2000: BioCoRE: A Collaboratory for Structural Biology Imaging Technology Group Forum, Beckman Institute

October 27-29, 2000: NCRR Biomedical Collaboratories Workshop Pittsburgh Supercomputer Center

4. Software Evaluation

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

The last software evaluation surveys we conducted for VMD and NAMD were in Aug. 2000 and some of the findings are below. The full NAMD and VMD survey reports as well as other evaluation reports are in appendix

Service: Software Evaluation

VMD and NAMD User Profiles, Aug, 2000

	VMD (884)	NAMD (129)
Academic users	81%	80%
Use for research	72%	80%
NIH funded	15%	11%
PC users	45% (Win)	65% (Linux)
Meets needs	92%	89%
Support meets expectations	96%	98%
Web-instructive	96%	94%
Satisfied overall	94%	96%

5. Lending out Expertise

Additional service activities the Resource engages in are

- User Support
- 12 Collaborations
- 9 Visitors
- 45 External Users, using 10% of local disk space

We seek to release code of high quality and low bug incidence, and our local users are extremely helpful in this respect. By prototyping our code they identify early on at

least the major bugs and assist us in assuring the quality of our products. Still our user population keeps growing and consequently we are expected to invest more and more resources in user support. When one has over 10,000 users, support becomes a major task and we take it very seriously. Only recently we revisited our support policies and adjusted them to both the growing demand and the growing number of software products we develop and maintain. The critical guidelines call for the programmers to respond to all support inquiries within 24 hours of receipt or next business day. Nontrivial inquiries may take longer, preferably no longer than 72 hours.

We emphasize assistance to biomedical researchers who would benefit from the use of our Resource's expertise for their research. In addition to the clear service value of the collaborations discussed earlier in this report, this last year we have had 9 visitors staying with us and we already agreed to host 4 new visitors in the next 6 months. The visitors typically fund their visit here and we supply the computing resources and the knowledge. These visits are beneficial to all involved.

6. Seminars 2000-01

In the past year we have had 21 Seminars organized and hosted by the Resource. Our seminars are an established institution on the UIUC campus and benefit students and faculty coming from Beckman and other UIUC departments. We bring to our campus, with some financial support from Beckman and our NIH Resource grant, leading scientists from around the country and all over the world. The seminars and abstracts are all posted on our web site at http://www.ks.uiuc.edu/Services/Seminar/ for easy information retrieval. Below is the complete list of the Resource seminars in the 2000-01 academic year

Spring 2001

January 29 **Albert-Laszlo Barabasi** University of Notre Dame The architecture of complexity: From the diameter of the www to the structure of the cell

February 5 **Ioan Kosztin** Physics and Beckman Institute, UIUC

Mechanical Force Generation by G-proteins

February 12 **Donald Engelman** Molecular Biophysics & Biochemistry, Yale University, New Haven, CT

Helix Interactions Inside Proteins

February 13 **Rienk van Grondelle** Faculty of Science, Vrije Universiteit Amsterdam

Ultrafast Excitation Energy Transfer in the LH1 and LH2 Rings of Photosynthetic Bacteria

February 14 **Nir Ben-Tal** Tel-Aviv University, Israel

ConSurf: An Algorithmic Tool for the Identification of Functional Regions in Proteins by Surface-Mapping of Phylogenetic Information

March 5 **Aihua Xie** Oklahoma State University, Stillwater, OK

Why does a photoreceptor protein need proton transfers for activation?

March 15 **Richard Neutze** Institute for Molecular Biotechnology, Chalmers University of Technology, Gothenburg, Sweden

Evolving Structural Rearrangements in Bacteriorhodopsin's Photocycle

March 19 **Ivo Hofacker** Institut fuer Theoretische Chemie, Austria

RNA Energy Landscapes and Folding Kinetics

March 30 **Sergei Izrailev** 3-Dimensional Pharmaceuticals, Inc. (informal seminar)

Computational Methods for Drug Discovery

April 9 **Evangelos Moudrianakis** Department of Biology, John Hopkins University

Architecture and Dynamics of the Protein Endoskeleton of the Gene

April 16 **John F. Marko** Department of Physics, University of Illinois at Chicago

Micromanipulation Study of Physical Properties of DNA and Chromosomes

April 23 **Russell M. Taylor** Department of Computer Science, University of North Carolina at Chapel Hill

The UNC nanoManipulator: Computer Scientists and Physicists Building Tools for Science and Education

April 30 **John P. Wikswo, Jr.** Department of Physics and Astronomy, Vanderbilt University

The Physics of the Heart: Optical And Magnetic Imaging of Cardiac Activity

Fall 2000

August 7 **Godehard Sutmann** Central Institute for Applied Mathematics, Research Centre Juelich Juelich, Germany (Informal Seminar)

The Nonlocaldielectric Response of Water and its Implications for Ionic Solvation and Screening

October 2 **Julio Fernandez** Mayo Foundation, Rochester, MN (co-sponsored by Molecular and Integrative Physiology)

Stretching Molecules into Novel Conformations Using the Atomic Force Microscope

October 5 **Rob Phillips** Brown University, Providence, RI (Informal Seminar)

Multiple Scale Challenges in the Modeling of Materials: Big Molecules and Small Solids

October 23 **Harel Weinstein** Department of Physiology and Biophysics, Mount Sinai School of Medicine

Computational experiments reveal signaling mechanisms in membrane proteins: From structural motifs to functional microdomains

October 30 **Boris Martinac** The University of Western Australia

Gating of MscL by Mechanical Force

November 13 **Gerhard Hummer** NIH

Helix nucleation kinetics from molecular simulations in explicit solvent

December 4 **Dave Thirumalai** Institute for Physical Science and Technology, University of Maryland Chaperonin-Mediated Protein Folding

December 11 **Robert H. Fillingame** University of Wisconsin Medical School Transmembrane Fo Sector of Rotary ATP Synthase: Structure and Mechanism

Training

1. Tutorials

We offer a variety of tutorials using a range of tools and media

- On-line
- Off-site
- Traditional
- Classes
- Graduate Students
- Postdoctoral Assoc

- Summer School Programs

In the past year we have significantly increased the training we provide. In addition to the visitors we train on site, we make our resources available to regular UIUC classes several times a year, to rotation students from various departments.

Our faculty participate in summer school initiatives bridging Physical and Life sciences. There are two off-site NAMD tutorials in preparation for NCSA and PSC (scheduled for June and August 2001 respectively). Information on both workshops and other training opportunities organized by the Resource are posted on our website at

http://www.ks.uiuc.edu/Services/Meetings_Tutorials/Tutorials/.

Distant tutorials were offered in the past year from Germany and Australia, taking advantage of our collaboratory environment BioCoRE. We offer online tours for BioCoRE and brief tutorials for VMD. These projects plan to develop much more extensive tutorials in the very near future. The BioCoRE team gave recently a brief tutorial in the UIUC Chemistry Department where they set up our first remote BioCoRE server. We are discussing with NCSA the possibility to offer a BioCoRE tutorial to their users.

Internal tutorials include a recent session offered on use of software development tools by scientists. Our web pages offer practical instructions on various useful subjects such as on writing and presentation skills, how to make movies, document conversion, use of publishing quality tools, web design and implementation.

We have purchased in the past year 70 new books that enhance the training and research value of our well stocked Resource library. We continue to subscribe to the following journals

- Physics Today
- Nature Structural Biology
- Science
- Nature
- Trends in Biochemical Sciences
- Structure with Folding and Design
- Biophysical Journal
- Sys Admin
- Journal of NIH Research

- MAC world
- C++ Report
- Chronicle of Higher Education
- Dr. Dobb's Journal
- Linux Journal
- Windows Developer's Journal

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

Recent PhD graduate are

1. Thorsten Ritz, Physics, Fall 2000, "The Quantum Physics of the Bacterial Photosynthetic Unit". Postdoctoral Associate at Oxford University, UK.
2. Ana Damjanovic, Physics, Spring 2001, "Quantum Physics of Photosynthetic Light Harvesting". Postdoctoral Associate at University of California at Berkeley.

2. Manuals and Tours

Our manuals have been available on the web for quite a while, they prove very useful and are regularly updated. BioCoRE has been experimenting with a new training concept — which combines an online tutorial with a slide tour. The 'tour' is regularly updated and developed but are we have yet to decide whether it justifies the efforts.

Dissemination

1. Publications

In the past funding period we have had

- 37 Refereed articles (see p. 73)
- Talks (PIs and other members as specified below)
- 15 Posters
- Brochures and Videos (see appendix and)

- Trade Magazines
- Printed Media
- Press Releases

In addition to articles published in scientific journals, to making the covers of prestigious publications (most recent ones in Biophysical J. and J. of Physical Chem) and presentation of talks and posters in professional meetings, the Resource this year has had quite a number of press releases and stories in popular media like the Chronicle of Higher Education, Dallas Morning News, The News Gazette (Champaign, IL), Supercomputer Center reports and more. All these news making stories are posted on the Resource web site in the In the News section at http://www.ks.uiuc.edu/Publications/stories.shtml .

Our Web site was selected by ISI for Current Web Contents.

The Resource PIs gave the following talks in the last funding period

Klaus Schulten

May 10, 2000 University of California, San Diego, Computational Sciences Seminar Series Keynote Speaker, "Steered computing - a powerful new tool for molecular biology"

June 6, 2000, Heidelberg, Germany, Workshop Innovations in Biochemical Visualization, "Visual and steered molecular dynamics"

June 6-11, 2000, Espoo, Finland, Sigrid Juselius Symposium, The Currents of Life - Electron and Proton, "Structure, dynamics and function of the purple membrane from Halobacterium salinarum"

July 5, 2000, Goettingen, Germany, Max-Planck Institute for Biophysical Chemistry Seminar Series, "Discovering the mechanical functions of proteins"

July 10, 2000, European Molecular Biology Laboratory, Heidelberg, Germany, EMBL Practical Course on Biomolecular Simulation, "Molecular Dynamics and Visualization"

"Molecular Dynamics with NAMD" (Training Course)

"Steered Molecular Dynamics"

July 13, 2000, Ringberg Castle, Rottach-Egern, Germany, Max Planck Society Workshop Biological Nanosystems, "Observation and multiscale modeling of biomolecular mechanics: how proteins pull and DNA coils"

July 25, 2000, NSF Headquarters, Arlingtion, VA, NSF Workshop Force Transduction in Biology, "Observation and simulation to study mechanical properties of proteins"

August 1-3, 2000, Gordon Research Conference on Molecular Electronic Spjectroscopy, "Migration of electronic excitation in photosynthetic chlorophyll-carotenoid aggregates"

August 13-17, Traverse City, MI, Protein Flexibility and Folding Workshop, "Observation and simulation to study mechanical properties of proteins"

August 19-20, 2000, Washington, DC, ACS Fall National Meeting, "Proton transport and pumping in the purple membrane of Halobacteria"

August 25-29, 2000, Graduate University of Advanced Studies, Hayama, Japan, Shonan Summer Lectures, "Photosynthesic apparatus in purple bacteria"

"Light harvesting in photosynthesis"

"Electron transfer in photosynthesis"

"From light absorption to ATP synthesis"

"Photosynthesis in Halobacteria/vision"

September 10-14, 2000, Litschau, Austria, Symposium in Theoretical Chemistry (STC) 2000 Plenary Lecture, "Quantum biology of light harvesting in photosynthesis"

September 14-19, 2000, Szeged, Hungary, 9th International Conference on Retinal Proteins, "Architecture and photodynamics of the purple membrane in a full-scale molecular dynamics study"

September 21-23, 2000, Washington, DC, SIAM Conference on Computational Science and Engineering, Plenary Lecture, "Challenges and opportunities for computational biology in the teraflop era"

October 19-21, 2000, Durham, NC, Third Triangle Biophysics Symposium, "Molecular dynamics investigations of titin and fibronectin unfolding"

October 27-29, 2000, Pittsburgh, PA, NCRR Principle Investigators Meeting, "The NIH Resource for biomolecular modeling and bioinformatics"

November 2-4, 2000, Washington, DC, 8th Foresight Conference on Molecular Nanotechnology, "Theory and modeling of biological nanodevices"

November 9-12, 2000, U. Texas Medical School, Galveston, Texas, Frontiers in Structural Biology of Membrane Proteins, "Molecular dynamics study of rhodopsin, bacteriorhodopsin and the purple membrane"

November 14-15, 2000, Mt. Sinai School of Medicine, New York City, Seventh Nemethy Symposium, New York Academy of Medicine in Manhattan, "Discovering the mechanical functions of proteins"

February 19, 2001, Wayne State University, Detroit, MI, "From Simplicity to Complexity and Back: Function, Architecture and Quantum Mechanical Mechanism of Light Harvesting Systems in Photosynthetic Bacteria."

February 28-29, 2001, Vrije Universiteit Amsterdam, Dept of Physics and Astronomy Amsterdam, The Netherlands, "Quantum biology of light harvesting in photosynthesis"

March 12-18, 2001, Basel, Switzerland Biozentrum, "Quantum biology of light harvesting in photosynthesis"

March 12-18, 2001, Monte Verita, Switzerland, Conference on Structure, Dynamics and Function of Proteins in Biological Membranes, "The energy conversion apparatus in purple bacteria – an integral view"

March 23, 2001, IBM T.J. Watson Laboratories Yorktown, NY, "Theory and Modling of Biological Nanodevices"

March 28, 2001, McMaster University, Hamilton, ON, Canada, "How Nature Harvests Sunlight"

April 3, 2001, ACS Meeting, San Diego, CA, "Multi-Scale Modeling of a Protein-DNA Complex"

April 13, 2001, Florida State University, Tallahassee, FL, "How Nature Harvests Sunlight"

May 22, 2001, 15th Darmstadt Molecular Modelling Workshop, Darmstadt, Germany, "Steered Molecular Dynamics - A Novel Method for Investigating Biomolecular Systems"

May 22, 2001, Max-Planck Institut duer Molekulare Physiologie, Dortmund, Germany, "Mechanical Force Generation by G-Proteins"

May 28, 2001, Technische Universitaet Berlin, Germany, "Physik der Photosynthese"

May 29, 2001, Freie Universitaet Berlin, Germany, "Static and Dynamic Disorder of the Exciton System in Light Harvesting Complexes LH2 of Purple Bacteria. The Role of Conical Intersection Topography on the Photoisomerization of Retinal".

Laxmikant Kale

IPDPS 2000 Conference; RTSPP and HIPS Workshops, Cancun, Mexico

IBM, T.J. Watson Research Center, Yorktown Hts. NY.

"Molecular Dynamics with Parallel Objects"

July 27, 2000

IBM, T.J. Watson Research Center, Yorktown Hts. NY.

"Blue Gene Roundtable Discussion"

August 9, 2000

SC'2000: (previously called Intl. conference on Supercomputing),

"Scalable Molecular Dynamics for Large Biomolecular Systems,"

Dallas, Nov 8 2000.

Todd Martinez

"Ultrafast Photochemistry from First Principles cis-trans Isomerization and Ring-Opening Reactions in Gas and Condensed Phases", Georgia Institute of Technology, April 2001

"Ultrafast Photochemistry from First Principles cis-trans Isomerization and Ring-Opening Reactions in Gas and Condensed Phases", University of Georgia, April 2001

"Ultrafast Photochemistry from First Principles cis-trans Isomerization and Ring-Opening Reactions in Gas and Condensed Phases", Emory University, April 2001

"Ultrafast Photochemistry from First Principles cis-trans Isomerization and Ring-Opening Reactions in Gas and Condensed Phases", Massachusetts Institute of Technology, March 2001

"First-Principles Chemical Reaction Dynamics Including Quantum Effects of Nuclear Degrees of Freedom", Frontiers of Theoretical Chemistry, Tokyo, Japan, March 2001

"Hybrid Quantum/Classical Methods for Atomistic Simulation", MIT/Harvard/Boston University Theoretical Chemistry Series, March 2001

"First Principles Reaction Dynamics on Ground and Excited Electronic States", Wabash College, February 2001

"Ultrafast Photochemistry from First Principles cis-trans Isomerization and Ring-Opening Reactions in Gas and Condensed Phases", California Institute of Technology, February 2001

"Ultrafast Photochemistry from First Principles cis-trans Isomerization and Ring-Opening Reactions in Gas and Condensed Phases", University of California at Los Angeles, February 2001

"Ultrafast Photochemistry from First Principles cis-trans Isomerization and Ring-Opening Reactions in Gas and Condensed Phases", University of Southern California, February 2001

"Ultrafast Photochemistry from First Principles cis-trans Isomerization and Ring-Opening Reactions in Gas and Condensed Phases", University of California at Santa Barbara, February 2001

"Ultrafast Photochemistry from First Principles cis-trans Isomerization and Ring-Opening Reactions in Gas and Condensed Phases", University of Pennsylvania, January 2001

"Cis-Trans Isomerization in Photobiology The Green Fluorescent and Photoactive Yellow Proteins", ACS Symposium on New Frontiers in Chemical Reaction Dynamics, Pacifichem, Hawaii, December 2000

"Photochemical Reaction Dynamics from First Principles", Notre Dame University, October 2000

"Chemical Reaction Dynamics from First Principles, Packard Fellows Meeting", Monterey, CA, September 2000

"Photochemistry from First Principles: Advances and Future Prospects, IUPAC Symposium on Photochemistry", Dresden, Germany, July 2000

"Multiple Spawning Approaches to Nonadiabatic and Tunneling Dynamics", Theory of Nonadiabatic Dynamics Workshop, Telluride, CO, July 2000

Robert Skeel

May 15, 2000, CECAM Workshop, Lyon, France,"Stability issues in symplectic integration"

Sep. 2000, First SIAM Conference on CSE, Washington, DC , "Methods for Biomolecular Dynamics,"

Nov 6, 2000, SCCM Seminar, Stanford University, California, "Multigrid methods for classical molecular dynamics"

Nov 15, 2000, Scripps Research Institute, San Diego, "Multigrid methods for classical molecular dynamics"

Dec 15, 2000, National Research Symposium on Geometric Numerical Integration Latrobe University, Melbourne, Australia, "Practical Evaluation of modified Hamiltonians"

Apr 4, 2001, ACS San Diego National Meeting, Symposium: Methods for Addressing Time- and Length-Scale Problems in Molecular Simulations, "Multigrid methods for classical molecular dynamics"

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

June 2000

USENIX 2000 Conference, San Diego, CA (Tim Skirvin)

July 2000

18th International Congress of Biochemistry and Molecular Biology, Birmingham, UK, "Elastic Rod Model of DNA Loops," (Alexander Balaeff)

August 2000

SciComp 2000 Workshop, San Diego, CA (James Phillips)

September 2000

First SIAM Conference on CSE, Washington, DC

"Multigrid N-body solvers," (Ismail Tezcan)

"Choosing Stepsizes for Molecular Dynamics," (David Hardy)

October 2000

International Workshop on Methods for Macromolecular Modeling, New York, NY "Choosing Stepsizes for Molecular Dynamics," (David Hardy)

Collaboratory workshop, Pittsburgh, PA (Robert Brunner, Kirby Vandivort, David Brandon, Gila Budescu)

November 2000

Foresight Conference, Bethesda, MD, "MD Study of Gold Binding Polypeptides," (Rosemary Braun)

Central Michigan University, Lansing, MI "Simulation of Structure and Function at retinal Proteins," (Emad Tajkhorshid)

SC 2000, Dallas, TX

"Scalable Molecular Dynamics for Large Biomolecular Systems," (James Phillips)

"BioCore/Faucets Demo," (Jay DeSouza)

"Scalable Molecular Dynamics for Large Biomolecular Systems," (Robert Brunner)

"Faucets demo, Namd Presentation," (Sameer Kumar)

(Joshua Unger)

"Scalable Molecular Dynamics for Large Biomolecular Systems," (Gengbin Zheng)

February 2001

Biophysical Society Meeting, Boston, MA

"Simulated Late Stage Refolding of Titin Immunoglobulin Domain,"(Barry Izralewitz), "Molecular Dynamics Study of Rhodopsin," (Emadeddin Tajkhorshid)

"ab initio QM/MM and Molecular Dynamics Study on Proton Pump Mechanism of Bacteriorhodopsin," (Shigehiko Hayashi)

"Simulated Late-Stage Refolding of Titin Immunoglobulin Domain," (Mu Gao)

"MscL Gating Studies by Molecular Dynamics Simulations," (Justin Gullingsrud) "Molecular Dynamics Study of Protein Interaction with a Crystal Surface," (Rosemary Braun)

"Dynamics of Electron Transfer Pathways in Cytochrome C Oxidase," (Ilya Balabin)

March 2001

American Physical Society meeting, Seattle, WA "Mechanical Force Generation by G-proteins," (Ioan Kosztin)

ACM Siggraph 13D 2001 Conference, Raleigh, NC

"A System for Interactive Molecular Dynamics Simulation," (John Stone)

"A System for Interactive Molecular Dynamics Simulation," (Justin Gullingsrud)

2. Outreach

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

- Major sites with link to us (132)
- Major sites that use our images
- Others publish our images
- On-site Demos
- Remote demos
- Open House 2001 (122 visitors)

Key sites with links to the Resource website include

Biophysical Society

http://www.biophysics.org

http://www.biophysics.org/biophys/society/misc/related.htm

Science Magazine

http://www.sciencemag.org/

http://www.sciencemag.org/feature/plus/sfg/resources/res_rschctr.html

Nanomedicine by Robert Freidas at the Foresight Institute

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

National Biomedical Computation Resource at San Diego Supercomputer Center

http://nbcr.sdsc.edu/

National Center for Research Resources at National Institutes of Health

http://www.ncrr.nih.gov

http://www.ncrr.nih.gov/ncrrprog/btdir/bt-d.htm

CMS Molecular Biology Resource at San Diego Supercomputer Center

http://restools.sdsc.edu/

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

Keck Computational Biology at Rice University

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

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

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

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

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

Biology Network Of Modelling Efforts at San Diego Supercomputer Center

http://bionome.sdsc.edu/

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

Bioinformatics and Computational Biology at George Mason University

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

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

BioMedNet

http://www.bmn.com/

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

BioInformer (A publication of European Bioinformatics Institute)

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

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

Center for Structural Biology at Yale University

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

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

Macromolecular Interactions Facility at University of North
Carolina-Chapel Hill

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

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

The Chemical Educator by Springer-Verlag

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

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

BioNews NetScan

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

http://www.scitari.de/BIONEWS/netscan.html

Science and Engineering Library at University of California at San Diego

http://scilib.ucsd.edu/

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

FRONTIERS IN BIOSCIENCE

http://www1.im.ac.cn/bioscience/current/currissu.htm

http://www1.im.ac.cn/bioscience/urllists/biology.htm

The Resource regularly receives, about once a week, requests for permissions to use Resource images on other sites, in textbooks to be published by others, in papers, and in talks to be given by others. We have formulated a standard response to such requests and while protecting our copyrights and ownership we have adopted an open and liberal approach in our permission granting.

III. More Efforts Benefiting Service, Training and Dissemination

Finally, there are the basic activities of the Resource that have direct effect on the scope and effectiveness of the service, training and dissemination areas. These include

- Quality Science
- Quality Technology
- User Surveys and Feedback Forms
- Program Friendliness and Accessibility
- Programmer Manuals and Documentation
- Software Available in Metacenters
- Software Available on Diverse Platforms
- Intellectual Property and Licensing

Most of these points have already been addressed in earlier parts of this report or earlier in this section. The last one, Intellectual Property and Licensing, however, was mentioned only in passing although it requires considerable attention almost on a daily basis. This includes formalizing code contribution to the Resource software by outside users and creating the agreements involved in order to regularize their integration; answering requests to distribute the Resource software with third-party products for either commercial or non-commercial purposes; satisfying Resource needs to integrate off-the-shelf

licensed tools in the Resource software; drafting licenses for new technological services produced by the Resource; ensuring that online distribution of Resource published material is in line with copyright laws; securing software keys and responding to vendor requests in accordance with university policies; and handling other related matters that are requiring more and more resources as the scope of the Resource's service and dissemination activities expands and the complexity of the relationship with an increasingly heterogeneous user population grows.

Last but not least the Resource organized an internal retreat on May 12-13. All Resource members participated, reviewed current activities and formulated research and development goals for the future.

Internal tutorials to improve members computational skeels and research qualifications are regularly offered. The most recent ones were on the use of development tools for daily research activities and a BioCoRE usage tutorial.

IV. Plans for Next Funding Period

- Exploiting Existing Opportunities
- Initiating the Use of Novel Means

We are committed to reach out and transfer our expertise and technologies by fully and systematically

- exploiting existing tools
- initiating the use of novel means

Extending and improving our *Administration*, *Service*, *Training* and *Dissemination* will better satisfy current and emerging needs of the biomedical community.

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2001 Advisory Board Meeting

NIH Resource for
Macromolecular Modeling and
Bioinformatics

Jeff Skolnick, Danforth Plant Science Center, Chair
Angel Garcia , LANL
Angela Gronenborn, NIH
Benoit Roux, Cornell
Marc Snir, IBM

Wednesday, May 2, 2001

8:00 Breakfast

8:30 Outlook for Renewal Proposal, K. Schulten

8:55 Modeling Tools: NAMD2 and NAMD3

* NAMD and Cluster Computing, J. Phillips (15min)
* NAMD: Multiscale Algorithms and Parallelization, L. Kale (15min)

9:25 Hybrid Quantum/Forcefield Methods for Biomolecular Modeling

* Charge Models, T.J. Martinez (10 min)
* Photodynamics, M. Ben-Nun (10 min)

9:45 Steered and Interactive MD, J. Gullingsrud

10:05 Coffee Break

10:30 Collaborative and Visual Technologies

* Advances in VMD: Improved Performance, Scalability, and Representation, J. Stone (10min)
* Towards Bioinformatics with VMD: Sequence Window, B.

Isralewitz (10min)
* BioCoRE Submits, Runs and Visualizes Your Simulation from Afar , K. Vandivort (10min)

11:00 Collaborations

* Mechanical Functions of Proteins (Collaborators: J. Fernandez, V. Vogel), M. Gao (10min)
* ATP Syntase (Collaborators: R. Fillingame, M. Wilce, W. Junge), I. Balabin (10min)
* Visual Receptors (Collaborators: E. Landau), E. Tajkhorshid (10min)
* Gold Binding Proteins (Collaborators: M. Sarikaya), R. Braun (10min)
* Glycerol Channel (Collaborators: R. Stroud), M. Jensen (10min)
* Lac Repressor (Collaborators: L. Mahadevan), A. Balaeff (10min)

12:00 Overview of Remaining Collaborations, I. Kosztin

12:15 Lunch

1:15 Service, Training and Dissemination, G. Budescu

1:45 Questions and Answers

2:45 Coffee Break

3:15 Closed Session and Report Preparations (Board Members)

6:00 Dinner (Board Members, PIs)

8:00 Reception at Schulten Residence (Board members, Resource members)