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ANNUAL PROGRESS REPORT (8/1/07 – 7/31/08)

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5. PRINCIPAL INVESTIGATOR:
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10. URL: `http://www.ks.uiuc.edu`
11. Was Patent or Copyright awarded this grant year: N
12. Total % effort related to AIDS research: 0%

Contents

General Description of Resource Operation:

The NCRR Resource for Macromolecular Modeling and Bioinformatics develops new methodological solutions for NIH researchers and others in the field of computational biomedicine. The researchers are offered atomic–level microscopic views of cellular processes that guide clinical research, as well as pharmacological and biotechnological development. The views provided, of static structures and dynamic processes, are obtained computationally by combining different experimental modalities, mainly from crystallography, NMR structure analysis, electron microscopy, atomic force microscopy, and single–molecule fluorescence, along with knowledge from physics and chemistry. The "computational microscope" is developed with very advanced concepts from computer science and introduces, through cooperation with various manufacturers and national facilities, the most recent computer technology to biomedicine as soon as it becomes available.

The computational methodologies developed and provided integrate structural and sequence data with mathematical and computational modeling. Advances are made available in the form of computer software that runs on a wide range of popular commodity computers as well as on the fastest computers at leading National Science Foundation centers or in development at manufacturers. Examples range from laptop computers running Windows, Linux, or Mac OS X, to commodity clusters, to the IBM Blue Gene machine with 40,000 processors. The two main Resource software programs, with over 118,000 registered users combined, are the molecular graphics and sequence analysis program VMD (Visual Molecular Dynamics) and the molecular dynamics program NAMD (Nanoscale Molecular Dynamics). Resource projects building on these programs offer the biomedical community research tools for structural biology and bionanotechnology. Users of Resource software receive extensive training in hands-on workshops and responsive service through email. Clinicians, bench scientists, and advanced modelers are served. Software and training material of the Resource are distributed free of charge through a much–visited web site.

The Resource has a long tradition in working closely with biomedical scientists at clinical and biomedical institutions. Without exception, all of the scientific projects conducted by the Resource involve collaborations with experimental groups, most of them at medical institutions. Currently active collaborations of the Resource include: investigations of blood clotting factors with researchers at Mayo Clinic; investigations of protein folding with researchers at the University of Illinois; investigations of ion channels with researchers at Chicago Medical School; and, investigation of the ribosome with researchers at the Howard Hughes Medical Institute (Columbia University).

During the past funding period, core activities (1-4) focused on the technological development of the four core development activities of the Resource:

(1.) The "structural systems biology" core development activity has seen significant progress over the past year. The very nature of living cells lies in the harmonious hierarchical assembly, regulation, and function of the cells' biomolecular building blocks. In the past, the Resource focused its research and modeling tool development mainly on the building blocks, but is now shifting its research to the whole cell level, developing modeling tools for structural systems biology. This shift is requiring existing tools to become more efficient in order to handle much larger structures, more automated in order to assist the modeler in building and analyzing models, and more comprehensive in order to address the modelers' wider range of tasks. Over the past year, development of a "Biomolecular Modeling Suite" for cell biology has progressed well: Coarse graining tools have been improved to aid in large system assembly; analysis tools have been improved to enable scientists to more easily visualize changes over time; molecule-building tools have been improved to permit more comprehensive modelling. Future plans include the development of tools for multiscale modeling and for combining multimodal experimental data, e.g. from nuclear magnetic resonance, crystallography, and electron microscopy.

(2.) The molecuar graphics core has seen its flagship program VMD for displaying static and dynamic structures, for sequence information, for structure generation and dynamic analysis to be further enhanced. VMD now makes more extensive use of graphics chips accelerated algorithms to achieve high performance for computationally demanding tasks, such as calculation of electrostatic fields surrounding molecular structures. VMD now supports improved analysis for the display of carbohydrate structures, implementing an improved version of recently described techniques [1]. Accuracy of root mean square structure alignment has been improved with the use of tighter error tolerance. Structure analysis routines in VMD have been updated to accommodate developments in the protein databank. User options for modification and customization of VMD have been enhanced. Finally, VMD has been updated with support for version 2.5 of the Python scripting language and version 8.5 of the Tcl scripting language, providing greater flexibility for user script development.

(3.) The molecular dynamics core develops the program NAMD. NAMD is a parallel molecular dynamics code designed for high–performance simulation of large biomolecular systems, and is used on massively parallel computers and other computer clusters by experimentalists and advanced modelers for both large- and small-scale modeling purposes. NAMD provides an "imaging tool" for biomolecular systems that is accessible to novice users such as experimentalists, triggers insights through hands-on interaction with the simulation, provides fast results by utilizing effectively the fastest supercomputers available, and is readily adaptable to the unique requirements of novel simulations such as those employing a mix of all-atom and coarse-graining techniques. The past year has seen improvements in the effective use of parallel scalability, including use of very large clusters. These enhancements have enabled ten-microsecond simulations, the larget all-

atom simulations realized today, involving a speed up of about a factor of 100 over prior routine simulations. NAMD has also been ported to the latest high-end platforms, the IBM BlueGene/P and the Cray XT4. Finally, NAMD now has preliminary support for graphics processing unit acceleration. Plans for NAMD development include extending simulation size and time scale via petascale computing, incorporation of new simulation methods, simplifying the process through which scientists can develop novel methods, and accelerating simulations with emerging performance technologies.

(4.) The "Biotechnology" core development activity furnishes tools and methods to assist researchers in nanodevice development. Biotechnology has the potential to revolutionize medicine, with computer modeling greatly accelerating the process of designing and testing synthetic biodevices. However, modeling tools and methods in biotechnology are significantly less developed than those available in mainstream life science. The core provides (i) methods and software for modeling silicon bionanodevices; (ii) methods for modeling carbon nanotube-biomolecular systems; (iii) coarse-grained descriptions of synthetic materials; (iv) methods to accelerate the design of artificial proteins; (v) tools for high-throughput management of simulations. Recently, the core has added a VMD toolkit for assembling models of bionanodevices. Since simulating bionanodevices requires different algorithms than simulating biomolecules, relevant features have been added to NAMD to perform device simulations: NAMD now supports force fields for atomic-level simulations of amorphous silicon dioxide, and allows devices to be represented implicitly by the electric fields they induce on the biomolecular regions of the simulation.

During the past year, the Resource continued to place strong emphasis on Collaborations, Service, Training and Dissemination.

Collaborations applied the Resource's most advanced modeling capabilities to medically relevant cellular systems investigated by leading intramural and extramural experimentalists. The Resource has completed last year 25 joint publications through these collaborations with experimentalists (in addition to 9 joint publications with extramural computational biologists). Currently, the Resource is engaged in 20 collaborations with experimental groups. The Resource adds on average one collaboration each month, and complets collaborations in a timely fashion.

Service is provided for the Resource software VMD and NAMD through responses to user inquiries, support of user groups, maintenance of program libraries, and provision of a visitor and training center as well as through an advanced computer laboratory. Over the last year downloads for VMD increased by 20,000, and for NAMD by 4,900. User support continued, with, for example, 4,800 exchanges sent to the VMD support email address. Over the last year 15 visitors received training at the Resources visitor center, and 24 seminars were organized. The Resource continues to offer technical advice, e.g., on building computer clusters and visualization facilities, to both external users and users

of our major software packages. The Resource has also overhauled its computational infrastructure, increasing the amount of available data storage on the local network to 112 terabytes.

Training has been and will continue to be available through on-site and online hands-on workshops, tutorials, and case studies. Over the past year, two workshops on computational biology were held, exploring physical models and computational approaches for the simulation of biological systems, one at the NIH campus in Bethesda and one at the Centre for Computational Materials Science in Bangalore, India. VMD and NAMD tutorials were updated and a new case study (on the light harvesting complex) was posted at the Resource web site. Future plans for training include continuing the face-to-face computational biophysics workshops, researching new technologies for enhancing online workshops, and writing new tutorials and case studies.

Dissemination is achieved primarily through the Resources highly visited web site, where the biomedical community can download software, access a variety of training materials, get electronic copies of the majority of Resource publications, and view research summaries and exemplary modeling projects. Over the past year, the Resource had 870,000 unique visitors to its web site, resulting in 2.0 terabytes of information transfer; the visitors downloaded over 21,670 publications from the Resource's online publications database. Dissemination also prospered in more traditional academic activities, including 55 articles in refereed journals or other publications, 45 talks by Resource PIs and 22 presentations by others; and 43 stories about the Resource posted in various media outlets. The challenge for the Resource over the next funding period will be to maintain its already high level of dissemination, without devoting more than the present (already extensive) level of resources to these pursuits.

Changes in Resource Direction:

The Resource, since its beginning 18 years ago, evolved its activities according to needs and opportunities in computational medicine. At the beginning of a new 5 year funding period and due to rapid developments in science and technology today, the last year has seen several changes in Resource activities.

As proposed in the renewal proposal and recommended by the review panel, the technology development effort has been reorganized into four cores: Structural systems biology, molecular analysis (VMD), molecular dynamics simulations (NAMD), and biotechnology.

As presented during the renewal site visit and enthusiastically endorsed by panelists, the Resource initiated an intense effort to accelerate NAMD through code execution on graphics processing units [2–4]. The effort has been extremely fruitful and today the Resource operates already a large number of computing platforms that integrate graphics processing units for simulations. The Resource, working closely with chip manufacturer

NVIDIA, foresees a huge potential for fast and extremely cost effective biological computing developing from graphics processing unit acceleration. This effort benefits tremendously from Resource expertise in both graphics and simulation programming; indeed NAMD acceleration through graphics processing units involves both VMD and NAMD developers.

As also proposed in the renewal proposal, the Resource moved its development effort towards petascale computing. A major development (petascale resource allocation committee, PRAC) proposal, submitted to NSF, is pending. A first, highly successful step has been taken that increased NAMD speed on parallel computing by nearly a factor 100 for routine calculations. The advance permits today 10 microsecond all atom molecular dynamics simulations. An application has been published already [5]; further applications are presently being completed. The development is widely seen as a revolution in computational modeling; the availability of petascale computers promises further dramatic advances that will render molecular modeling more relevant than ever.

As also presented at the site visit and endorsed by the panel, the Resource initiated a very important structure analysis method, molecular dynamics flexible fitting, that combines crystallographic and electron microscopy data to retrieve high resolution structures from electron microscopy data. The method, applied to the ribosome as a test case and recently published [6], fits high resolution crystallographic structures, often only representing non-functional states of biopolymers, into lower (but better than 10 Angstrom) resolution electron microscopy maps that represent functional states. The combination of methods promises a great advance in structural systems biology since it applies to very large structures. Several key collaborations of the Resource build on the new development.

Lastly, the Resource has become a founding partner of an intramural research center for the physics of living cells that combines mainly experimental scientists with the Resource. A proposal to NSF for a Physics Frontier Center went successfully through several stages to become a finalist, the funding decision being pending.

Impact of Resource on Biomedical Research:

The great impact of the Resource on biomedical research is evident in the very large number of registered users of its software, the high number of citations of its publications, its publication record, and the number of accesses of its web site (see above).

The Resource is known for producing high-quality computational technologies that combine structural and sequence data with mathematical and computational modeling, specifically its software applications VMD and NAMD. Acknowledgment from the biomedical community of the utility and quality of Resource software is provided by the number of registered downloads over the lifetime of the software and over the last year (figures are rounded): 20,070 new VMD downloads (108,835 total), and 4,941 new NAMD downloads

(25,197 total). Repeat downloads from users who have downloaded more than one version of a software application, run at around 18% for VMD and NAMD. Data across recent user surveys (2005 - 2006) indicate that the majority of users are affiliated with academic institutions (88%), use Resource software for research (86%), and just over one-fourth (26%) are NIH-funded. Survey results further indicate a high degree of satisfaction, with majorities of VMD (94%) and NAMD (77%) users agreeing or strongly agreeing with the statement "I am satisfied" with the indicated software.

Citations by others of Resource publications are another indication of impact on the biomedical community. A search of the Thompson ISI citations database in April 2008 returned nearly 21,000 citations of papers published by the Resource since 1989. The VMD and NAMD source papers received 2,500 and 900 citations, respectively, with 600 and 260 citations, respectively, in 2007. Journals with citations of Resource publications in the May 2007 – April 2008 period include Cell, Structure, Science, EMBO Journal.

Highlights

High-Performance Computing with Graphics Processor Clusters (SPID 0050)

Modern video games running on state-of-the-art personal computers achieve incredible levels of graphical detail and realism. This is due not to the speed of the main processor on the motherboard, but to the specialized graphics processing unit (GPU) on the video card. While older GPUs could accelerate only a few, strictly specified calculations using dedicated processing hardware, the modern GPU is increasingly flexible and programmable. This allows the graphics programmer to describe complex visual effects such as smoke, fire, and blowing hair as algorithms that run on the GPU, leaving the main processor free for other tasks. With a million pixels and thousands of objects to draw, the graphics workload can be broken into thousands of independent tasks and run simultaneously on hundreds of processing elements. This high degree of parallelism has allowed GPU designers to extract maximum performance from each new generation of microprocessor fabrication technology, yielding exponential performance growth. As a result, scientific visualizations that used to require expensive graphics workstations are now achievable with commodity video cards.

Due to their specialized design, graphics processors hold a sustainable factor of ten advantage over traditional processors in peak performance. With scientific computing ever hungry for increased capability, a new generation of general purpose GPU programming languages (e.g., the NVIDIA CUDA programming language) has now emerged to allow the power of programmable graphics processors to be harnessed for non-graphics tasks. In these languages, parallelism is explicitly exposed by the programmer, allowing efficient use of the computational units on the GPU. For this reason GPUs often achieve performance ten to one hundred times that of a traditional processor when used for general purpose scientific computing. Just as commodity video cards have freed the biomedical researcher from expensive graphics workstations, they may now provide an inexpensive source of computational power, either replacing large and complex compute clusters or greatly enhancing their power.

The Resource produced an early paper [2] demonstrating the utility of the NVIDIA CUDA programming language to harness the power of modern GPUs for both preparing and conducting molecular dynamics simulations of large biomolecular systems using the Resource's popular software packages VMD and NAMD.* Seeking new applications, the Resource has recently applied GPU computing to fluorescence microphotolysis, a non-invasive method of studying dynamics of cellular components using optical microscopy [7]. In this method, a small area of a fluorescent specimen is illuminated by a focused laser beam, and the fluorescence of the illuminated spot is recorded. Analyzing the change of

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

the fluorescence signal with time, one can extract diffusion constants of the fluorescent molecules by solving a diffusion-reaction equation (a partial differential equation in time and 2D or 3D space). With a simple, unoptimized implementation, this computation that previously took 8 minutes has been shown to run in 38 seconds on a GPU. Given that experimentalists need to perform multiple computation runs with various parameters to match the observed fluorescence signals, this 12-times speed-up is very welcome. This application of GPU computing also opens new possibilities for high-resolution microscopes with intricate patterns of light distribution that require expensive calculations to analyze.

Figure 1: Cluster of 64 graphics processors at NCSA.

Although many CPUs are required to match both the peak and generally achieved performance of a single GPU, in order to address the most challenging scientific computing tasks clusters of GPU-accelerated machines must be employed. To support the development of applications for such clusters, the National Center for Supercomputing Applications (NCSA) has recently installed a 16-node InfiniBand cluster with four NVIDIA GPUs and two dual-core processors per node. The Resource was able to demonstrate a factor of five overall speedup from GPU acceleration when running a million-atom NAMD[†] simulation on the entire cluster, performance equivalent to hundreds of traditional processors. This implementation benefits from recent improvements that allow calculations running on the GPU to overlap with communication and other unaccelerated calculations. Further improvements to performance on GPU clusters will come from the tuning of CPU calculations that previously had negligible impact on performance, but limit performance when the majority of the calculation is done on the GPU.

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

Ten-Microsecond Simulation of Protein Folding (SPID 0004)

Predicting the folding mechanism and folded structure of a protein from its amino acid sequence is one of the most important problems in structural biology. A better theoretical framework describing the protein folding process would both aid in the understanding of diseases caused by point mutations in proteins, and allow the design of protein variants with novel function. Computer simulations using techniques such as molecular dynamics (MD) can be used to study the process of protein folding, but until now complete simulations of the folding of a protein were inaccessible even to modern supercomputers. While several approaches, including Monte Carlo structure prediction [8] and the use of a large number of short MD trajectories [9], have been applied to the protein folding problem, long timescale molecular dynamics trajectories offer significantly more information because the folding process can be observed over realistic timescales.

Downhill-folding mutants of several proteins which fold on timescales of 1-5 μs are currently known, and offer an ideal target for MD simulations aiming to observe complete folding trajectories of proteins which can be compared to experiment. Microsecond simulations currently represent the upper limit of timescales accessible to molecular dynamics, and require the application of substantial computing resources and optimization of the simulation software and parameters. However, the wealth of information on the protein folding process that would be provided by such a clear comparison between experiment and theory makes the simulation of these proteins an important opportunity.

NAMD (Nanoscale Molecular Dynamics)* is a parallel molecular dynamics code designed for high performance simulation of large biomolecular systems [10, 11]. NAMD employs the prioritized message-driven execution capabilities of the Charm++ parallel runtime system,† allowing excellent parallel scaling on both massively parallel supercomputers and commodity workstation clusters. NAMD is distributed free of charge to over 25,000 registered users as both source code and convenient precompiled binaries.

NAMD has enabled some of the largest biomolecular simulations attempted, including a multi-million-atom, thousand-processor simulation of the ribosome at Los Alamos National Laboratory as early as 2003. In 2005, NAMD was used for the first all-atom simulation of a complete virus, the Satellite Tobacco Mosaic Virus (STMV) [12]. This million-atom simulation was limited by available resources to a mere 50 ns, but was still sufficient to propose a possible assembly pathway.

The simulation of smaller molecules for longer times is significantly more challenging to parallelize efficiently than larger simulations, since the amount of independent work per

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

†URL: `http://charm.cs.uiuc.edu/`

processor at each iteration is smaller. To address this challenge, it was necessary to go beyond the traditional NAMD performance goal of running any simulation well on any number of processors with little guidance from the biomedical end-user. Instead, a simulation-specific tuning approach was taken, selecting through insight and experiment the processor count best suited to the parallel decomposition of the simulation. Instrumented benchmark runs were inspected with the Charm++ Projections performance visualization tool, identifying parallel bottlenecks and inefficiencies to be addressed. One insight was to move the communication-intensive calculation of electrostatic interactions to dedicated processors, spread across the machine, such that at each communication stage a processor was never both sending and receiving data.

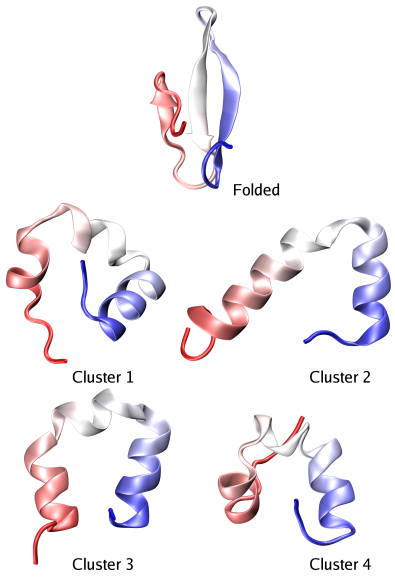

Figure 2: Folded and partially folded conformations of the "WW domain" protein.

The improved NAMD was applied to simulate a fast-folding mutant of the Pin1 WW domain [13], a small protein used frequently in experimental folding studies. A simulation rate of 100 ns per day was achieved on 47 nodes of the Abe cluster at NCSA [14]. Three WW domain trajectories were generated, of durations 10.0, 2.0, and 1.5 μs. In all three cases the protein folded into an incorrect structure after a series of intermediates, likely indicating a failure of current MD forcefields to accurately treat the folding of all proteins. Ongoing simulations using proteins other than the WW domain have, however, been more successful. The achievement of the simulation timescales necessary to observe protein folding events in molecular dynamics simulations marks an important first step, but the promise of this method will only be realized through further work to refine existing MD models.

Grant Number: P41RR05969 (8/1/07 – 7/31/08)

Gating of a Mechanosensitive Channel (SPID 0034)

The perception of sound and regulation of blood pressure or cell volume are typical examples of biological processes mediated by mechanosensitive (MS) ion channels *. These channels open and close in response to stress conveyed through the cytoskeleton or the cellular membrane [15–17]. In bacteria, mechanosensitive channels have been proposed to act as safety valves facilitating the release of small solutes, thereby preventing the cell from bursting upon osmotic shock [18–21]. The gating mechanism of these channels, however, remains to be fully determined.

While the identification and characterization of eukaryotic mechanosensitive channels has been rather slow [17], two bacterial channels have been widely studied and recently crystallized: the mechanosensitive channel of large conductance, MscL [22, 23] and of small conductance, MscS [18, 24–26]. The latter channel is also found in archaea and plants [27, 28] and has become the focus of experimental and theoretical studies since it may represent an archetypal mechanosensor.

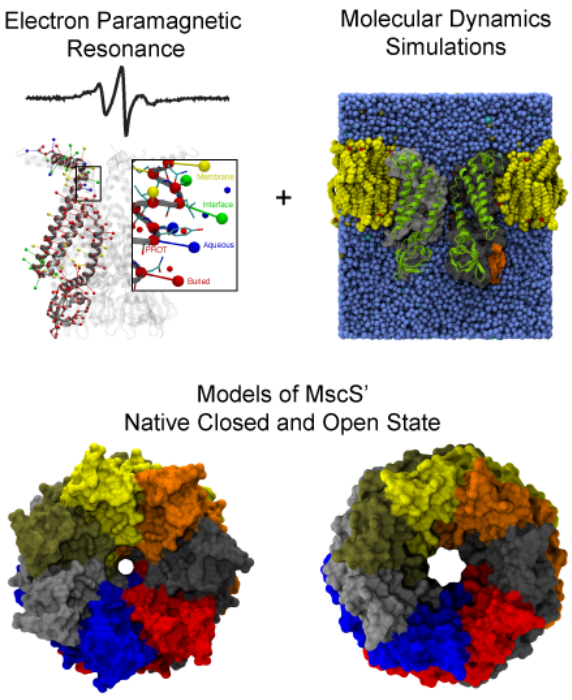

Figure 3: Molecular dynamics simulations enable the refinement of three dimensional models of the mechanosensitive channel of small conductance MscS. The models of MscS were obtained by incorporating experimental data from electron paramagnetic resonance (EPR) measurements as restraints in simulations [29].

Obtaining the crystal structure of MscS was a fundamental step towards the characterization of the MscS gating mechanism and the understanding of mechanotransduction in

*URL:http://www.ks.uiuc.edu/Research/MscSchannel/

living cells at the molecular level. However, many questions remain unanswered and new ones have arisen: Does the crystal structure show a closed or open conductance state? What residues are relevant for gating? Does the structure reveal the physiological role of MscS, e.g., is MscS only a safety valve?

In order to answer these questions, the Resource performed extensive molecular dynamics simulations of the MscS protein embedded in a fully hydrated membrane bilayer (230,000-atom systems). The simulations, altogether lasting hundreds of nanoseconds and only possible to realize through the use of the Resource software package NAMD, permitted a thorough characterization of the MscS conductance *in silico* [30–32]. The Resource teamed up with Dr. Eduardo Perozo (U. Chicago) to compare the outcome of the simulations with electrophysiological measurements that unambiguously determined the conductance of MscS *in vitro* [32]. The combined effort led to conclude that the MscS crystal structure represents an intermediate state between open and closed conformations.

The collaboration with Dr. Perozo was extended to incorporate electron paramagnetic resonance (EPR) measurements into models of MscS. The EPR data was used as restraints that guided molecular dynamics simulations of MscS, resulting in models of MscS in its closed and open conformations [29] (Vasquez, V., M. Sotomayor, J. Cordero-Morales, K. Schulten, E. Perozo. *Submitted*, see Fig. 3).

The combined experimental-computational [29, 32] effort pinpointed key interactions between protein residues that were later on corroborated by mutagenesis [33]. Moreover, computational modeling suggested a gating mechanism [32] that is in agreement with recent experimental results [34]. The new open and closed models based on experimental data [29] will certainly guide the design of future simulations and experiments testing the function of MscS and other mechanosensitive channels at the cellular level. Indeed, Resource scientists are now testing whether glutamate, a well-known osmoprotectant in bacteria, can pass through or can be filtered out by the MscS's transmembrane and cytoplasmic domains.

Ribosome (SPID 0042)

The translation of genetic information into protein sequences is essential for life. This process begins with the transcription of genomic DNA into mRNA, which in turn is translated into proteins using the genetic code. At the core of the translation process lies the ribosome, one of the largest and most complicated molecular machines known, where protein synthesis takes place in every cell [35]. Due to its fundamental role, the ribosome is a major target for drug discovery and design; many antibiotics in clinical use block protein synthesis in the bacterial ribosome [36]. The structure and function of the ribosome are fascinatingly complex. Two thirds of the ribosome consist of ribosomal RNA (rRNA), while over 50 ribosomal proteins make up the rest. The process of translation involves many steps, including decoding and proofreading that insure the right amino acid is incorporated, and peptide bond formation. At each step, the ribosome interacts with additional auxiliary factors and undergoes large conformational changes to perform different functions. High-resolution structural information of these functional states is central to understanding the mechanisms of translation.

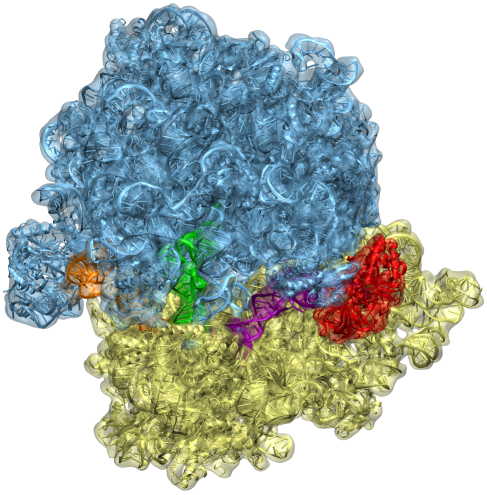

Figure 4: Fitting an atomic structure of the *E. coli* ribosome into a cryo-EM map of a ternary complex-bound ribosome at 6.7-Å resolution by means of MDFF. The atomic structure reveals in unprecedented detail the interaction of the factors with the ribosome, shedding light into a key step to translate genetic information into protein with high fidelity.

Over the past few years, landmark progress has been made towards obtaining structural data of the ribosome thanks to both cryo-electron microscopy (cryo-EM) [37] and X-ray crystallography [38]. Cryo-EM offers snapshots of the ribosome in functional states [39–44], currently with resolutions of 7–12 Å, still lacking atomic detail. This data is complemented by X-ray crystallography, that provides atomic resolution for most of the ribosome [38, 45, 46]. However, the X-ray structures do not represent functional intermediates of the ribosome, due to the non-natural conditions needed to form crystals.

Computer simulation offers a means to bridge the resolution gap between crystallography and electron microscopy, by *flexibly fitting* X-ray structures into cryo-EM maps. The calculations provide atomic structures of the ribosome in different functional states. The ribosome represents a challenge to fitting methods due to its sheer size. In the past year, in collaboration with Joachim Frank (HHMI), a leader in the field of cryo-EM, the Resource developed the molecular dynamics flexible fitting (MDFF) [6]* and applied it to the ribosome.

The Resource has obtained with MDFF twelve structures of the ribosome at different stages of translation. The atomic-resolution structures reveal the interactions between the ribosome and its factors in unprecedented detail. For example, MDFF provided an atomic structure that throws new insight on how the ribosome recognizes the right amino acid encoded in the genetic message. Moreover, the role of the participating factor, the ternary complex, can now be studied at a new level of detail. The various structures can be utilized by the research community, thus providing invaluable data for not only determining the mechanisms of translation but also for the design of new experiments and antibiotics. Resource scientists collaborate with Taekjip Ha (UIUC) using its atomic structures of the ribosome also to suggest target locations for fluorescent probes monitoring ribosome dynamics.

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

Nucleotide Transportation by a Mitochondrial Carrier (SPID 0057)

Adenosine triphosphate (ATP) is the fuel during manifold processes in all living cells. In the human body, ATP is produced from the oxidation of carbohydrates, such as sugar and fat. Its hydrolysis provides energy to drive numerous metabolic reactions that otherwise could not occur. For instance, ATP hydrolysis provides energy for many of the pumps that transport substances in and out of the cell [47]. It also powers the molecular motors that enable muscle cells to contract [47].

The synthesis of ATP from adenosine diphosphate (ADP) involves a series of delicate chemical reactions, with the final steps taking place inside the mitochondria in eukaroytic cells. During these reactions, ATP is synthesized by joining an ADP with an inorganic phosphate. ATP is then exported to the cytosol where its hydrolysis releases the energy stored in the molecule. On the other hand, ADP, the product of ATP hydrolysis, is shuttled back into the mitochondria for the next round of ATP production. The exchange of ADP and ATP across the mitochondrial membrane is crucial for the continuous production of ATP. This exchange is mediated by a membrane protein named ADP/ATP carrier. ADP and ATP are exchanged by the carrier across the mitochondrial membrane with a 1:1 ratio.

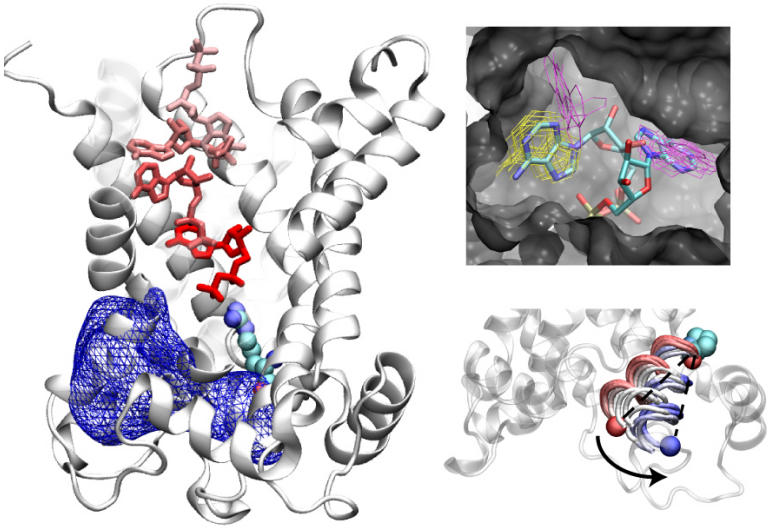

Figure 5: The ADP binding process (left) and ADP binding site (right top) revealed by molecular dynamics simulations. Initial conformational changes of the protein (right bottom) involved in the nucleotide translocation revealed by steered molecular dynamics simulations.

During an exchange cycle, the carrier switches between two states: a cytosolic-open state (c-state), to which ADP binds, and a matrix-open state (m-state), to which ATP binds [48]. Since the only available crystal structure is that of the c-state carrier [49],

conformational transitions of the protein during its exchange cycle are largely unknown. Furthermore, as the crystal structure is in complex with an inhibitor, the binding site of the substrate ADP inside the carrier lumen remains elusive.

In order to explore the binding site of ADP and probe the conformational transitions of the carrier during nucleotide translocation, the Resource performed extensive (over 300 ns) molecular dynamics simulations on the carrier [50]. These simulations revealed rapid, spontaneous binding of ADP to the carrier lumen. This is the first example of a complete ligand binding event described in full atomic detail using unbiased simulations [50]. Two putative ADP binding sites, deeply positioned within the lumen, are revealed by the simulations (Fig. 5). An unusually strong positive electrostatic potential of the protein is found to be the driving force of the observed rapid binding of ADP. This positive potential, which allows the carrier to recruit the negatively charged substrate ADP, is likely a common attribute among the entire family of mitochondrial carriers, as revealed by sequence analysis of over 1,000 membrane proteins [50]. As the substrates of mitochondrial carriers are often negatively charged, the positive potential can play a key role in substrate recruitment and translocation of these carriers [50].

Using steered molecular dynamics, a technique pioneered by the Resource, scientists also probed the conformational changes of the carrier during nucleotide translocation. The simulations reveal that through rearrangement of salt bridges at the bottom of the lumen, ADP binding and translocation can trigger outward movements of transmembrane helices of the carrier, thus, unlocking the protein, allowing it to expand (Fig. 5). These results shed light on key structural elements of the carrier involved in the nucleotide trasnportation cycle [50].

Subprojects

BTA UNIT: C

TITLE: Simulation Tools for Biotechnological Nanodevices

KEYWORDS: biotechnology, nanodevices, carbon nanotubes, molecular modeling

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ABSTRACT: This development project deals with the application of biotechnological nanodevices made from or working in conjunction with biological materials to solve a diverse set of technological problems, leading to new ways to understand biology and diagnose or treat disease. Engineering such devices often requires the testing of many prototypes before the best solution is found for a particular problem. Computer modeling provides a means for evaluating many potential designs, so that only the most promising need to be physically built and tested. The Resource has focused on several areas of biotechnological nanodevice simulation (http://www.ks.uiuc.edu/Research/Categories/Nano/). Methods for visualizing and modeling silicon bionanodevices, for example, will allow the techniques used in fabricating computer chips to be employed in building bio-electronic sensors. Such sensors could be produced cheaply, providing an inexpensive method to implement electronic "tweezers" for examining single molecules. Another promising technology is the use of carbon nanotubes, which are synthetic materials with properties that enable their use for in vivo sensing, e.g., of the action of agents used in chemotherapy of cancers. However, simulating devices and materials such as these can be a prohibitively expensive computational undertaking. Accordingly, the Resource is pursuing coarse-grained methods for simulating synthetic materials such as detergents, nanotubes, and silica, which will open up new opportunities for modeling new nanodevice designs [51].

Several tools have been developed in the last year to simplify setting up simulations of silicon-based nanodevices, many of which are embodied into the Resource's molecular visualization tool, VMD, through an Inorganic Builder plugin. The plugin includes tools for specifying the geometry of nanodevice models composed of any one of several crystalline and amorphous materials. Other tools allow such models to be combined with models of biomolecules and physiological solution.

Due to its well-understood properties and mature manufacturing technology, amorphous silicon dioxide is a material of particular interest for nanodevices. Modeling this material using classical molecular dynamics requires a different force field model than that used for normal biological materials. The BKS force field [52] is a force field model for amorphous silicon dioxide, and has recently been added to the Resource's molecular dynamics package, NAMD.

One method for simulating the affect of a nanodevice's electronic structure on a biomolecule is to impose the electrostatic field of the device in an all-atom molecular dynamics simulation of the biomolecule. Such continuous fields can be approximated by discrete values on a grid. A device is modeled by superimposing the fields induced by different parts of the device to determine the total force influencing the behavior of the biomolecule. In the last year, NAMD, has been extended to permit

simulation using multiple grids applied to different subsets of atoms in a simulation, allowing virtual testing of more complex devices. [53]

BTA UNIT: C

TITLE: Nucleotide Transportation by a Mitochondrial Carrier

KEYWORDS: ADP/ATP carrier, nucleotide transportation, nucleotide binding

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ABSTRACT: The hydrolysis of adenosine triphosphate (ATP) provides energy for numerous metabolic reactions in a cell. In eukaryotic cells, ATP is synthesized inside the mitochondria from adenosine diphosphate (ADP) and inorganic phosphate. The newly synthesized ATP is then exported to the cytoplasm to be consumed, while cytosolic ADP is imported to the mitochondria for ATP regeneration. The exchange of ADP and ATP across the mitochondrial membrane is mediated by the mitochondrial ADP/ATP carrier, a membrane protein which has been proposed to cycle between two conformationally distinct states, cytosolic-open (c-state) and matrix-open (m-state), thereby shuttling nucleotides across the inner mitochondrial membrane (http://www.ks.uiuc.edu/Research/AdpAtpCarrier/). The c-state of the carrier is the only structurally known state [49]. As a result, conformational changes of the carrier involved in an exchange cycle remained elusive.

In order to explore the binding site of ADP and probe the conformational transitions of the carrier during nucleotide translocation, the Resource has performed extensive molecular dynamics simulations totaling over 300 ns [50]. Such long simulations performed on a system over 100,000 atoms are only made efficient by the recently improved parallel performance of NAMD [11]. These simulations revealed rapid, spontaneous binding of ADP to deeply positioned binding sites within the carrier lumen. A strong positive electrostatic potential is found in the lumen, which constitutes the main driving force for the observed spontaneous binding of ADP. Analysis of 34 yeast mitochondrial carriers as well as over 1,000 other yeast membrane proteins indicates that the positive electrostatic potential is likely a common

attribute among the entire family of mitochondrial carriers [50]. In addition to playing a key role in substrate recruitment and translocation, the net positive charges of mitochondrial carriers might also be critical for their binding to the negatively charged environment of the inner mitochondrial membrane.

In order to probe further structural changes that might be involved in activation of the carrier, ADP was forced to penetrate deeper beyond its binding pockets by steered molecular dynamics simulations. The results reveal that through rearrangement of salt bridges, ADP binding and translocation can induce the outward displacement of three transmembrane helices. During this process, salt bridges connecting these helices are either weakened or completely broken, which "unlocks" the helices and allows the matrix-exposed portion of the protein to open. These results shed light on key structural elements and initial steps involved in the conformational transitions of AAC in a nucleotide transportation cycle [50].

BTA UNIT: S

TITLE: Computational Facility

KEYWORDS: parallel computing, visualization, network

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ABSTRACT: The last year has seen major improvements to the Resource's computational facility (http://www.ks.uiuc.edu/Development/Computers/).

The Resource scientists enjoyed an unprecedented four-fold increase of computational resources last year. A large part of this increase came from the National Science Foundation (NSF) funded National Supercomputing Centers. The total number of Service Units (http://www.ks.uiuc.edu/Development/Computers/nrac.html) awarded to the Resource by NSF's Large Resource Allocations Committee has more than doubled compared to last year, increasing to a total of 20.4 million service units (2336 CPU-Years). The Resource has also been awarded 14.1 million service units (1615 CPU-years) through the Institute for Advanced Computing Applications and Technologies funded by the State of Illinois. These allocations are supplemented by the 300 processors on the Resource clusters.

In pursuit of continued technological developments for high performance molecular dynamics simulation, the Resource has purchased an 8-node graphics processing unit (GPU) cluster for use in developing GPU-accelerated versions of the NAMD (http://www.ks.uiuc.edu/Research/namd/) and VMD (http://www.ks.uiuc.edu/Research/vmd packages distributed by the Resource. Support for the general software development

and testing activities of the Resource has recently been bolstered with the purchase of 10 Sun Ultra 24 workstations, and 11 Apple Mac Book Pro laptops with advanced graphics systems that can now also be used for computation as well as for molecular graphics.

The drastic increase in available compute power required a shift of the investments in hardware and services of the Resource computational facility. This shift, namely from simulation hardware to data storage and data analysis hardware, had been already foreseen in the renewal proposal. Accordingly, the Resource has recently increased the amount of available data storage on its local network from 64 TB to 112 TB. This was achieved through the purchase of a Sun X4500 server, containing 48 1 TB hard drives, capable of serving the data directly to the entire network. Additionally, through the use of the ZFS file system, this space is significantly more flexible than what was previously available.

The resource has recently begun construction of a GPU-accelerated cluster for use development and testing of the GPU accelerated versions of NAMD and VMD. The new cluster consists of 8 Sun Ultra24 host machines, each containing an NVIDIA 9800GTX GPU. The cluster uses an InfiniBand interconnect for high bandwidth and low latency communication. The GPU cluster will also support next-generation GPU devices featuring double-precision floating point arithmetic.

BTA UNIT: C

TITLE: The Mechanical Strength of a Blood Clot

KEYWORDS: fibrinogen, protein mechanics, thrombosis, stroke, cardiovascular disease, cerebrovascular accident

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ABSTRACT: Regeneration and protection of the cardiovascular system is essential for vertebrates. Blood clots form part of the emergency response to an injured blood vessel; they surround the damaged tissue stopping bleeding and blocking invasion by foreign pathogens. On the other hand, blood clots can restrict essential and normal blood flow if they form at the wrong place, or break free from a larger vessel only to later block a smaller one (thrombosis) [54]. This manifests in well known cardiovascular events such as heart attacks, strokes, and pulmonary embolisms. An inportant aspect of blood clots' role in health and disease is their mechanical elasticity. Blood clots must be stiff enough to seal wounded vessels, yet flexible to prevent breakage and subsequent blockage of small vessels [55].

Blood clots are built from red blood cells and a protein called fibrinogen. In its active form, fibrinogen is converted by thrombin into fibrin, which polymerizes into a branched network to form a hemostatic plug in combination with platelets and blood clotting factors [56, 57]. The mechanical properties of blood clots are highly dependent on both the network architecture of fibrin and the mechanical properties of fibrin's individual components [57].

Interactions between paired chains of fibrin and fibrinogen have been described by several recent studies that stretched these molecules using both optical tweezers [58–60] and atomic force microscopy (AFM) [61]. However, the elastic properties of single fibrinogen molecules and their coiled-coil helices, the predominant structures along the length of the molecule, remain unclear.

A key step in the characterization of fibrinogen's elasticity has been achieved last year by the Resource. Using steered molecular dynamics (SMD) simulations, a technique pioneered by the Resource [62], the mechanical strength and unfolding pathway of fibrinogen was probed. The simulations performed, involving over 1 million atoms for over 50 nanoseconds, were the largest and longest SMD simulations ever attempted. Long-range electrostatic interactions were computed using a novel parallel implementation of the particle mesh Ewald method (pencil decomposition), which permitted efficient use of a large array of 1024 and 2048 processors. The simulation results permitted definitive interpretation of atomic force microscopy data obtained by the Resource collaborator (B. Lim, Mayo Clinic) and explained, at the molecular level, how fibrinogen is capable of buffering significant mechanical force in blood clots. Specifically, the simulations revealed that a particular region of fibrinogen, called the coiled-coil domain, consisting primarily of alpha helices, extends sequentially and confers elasticity to the molecule. This insight opens new avenues for treatments to control the incidence of blood clot pathologies. For example, it was found that pH and calcium concentrations alter the stiffness of blood clots, thereby opening pharmacological avenues for controlling the incidence of pathological blood clots. This work, completed over the past funding period, has been recently published [63]. (see also http://www.ks.uiuc.edu/Research/fibrinogen/).

BTA UNIT: C

TITLE: 10 Microsecond Simulations of Protein Folding

KEYWORDS: Your subproject keywords

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ABSTRACT: One of the most significant advances in computational biology today deals with the protein folding problem: how the sequence of a protein specifies its folded structure (and thus, function). Efforts to study the folding process of proteins computationally are hampered by the fact that protein folding generally requires tens of microseconds or longer, periods which until recently were unattainable through simulation. However, thanks to extremely fortunate advances in parallel molecular dynamics simulations, the full folding process of proteins can now be studied computationally (http://www.ks.uiuc.edu/Research/folding).

The Resource has begun to study the folding processes of three small, fast-folding proteins, namely villin headpiece, lambda repressor, and the Pin1 WW domain. These proteins are simultaneously being studied experimentally by resource collaborator Martin Gruebele. In an appropriate solvent environment, studying each of these proteins using molecular dynamics requires simulation of 30,000 atoms for 5-10 microseconds. Using the improved NAMD [11,14], these simulations can be efficiently performed now on 330 processors, at a rate of 100 ns/day, an unprecedented computational speed.

A series of simulations of the alpha helical villin headpiece showed the complete folding process occurring in 4-6 microseconds, and preliminary data on lambda

repressor show formation of proper secondary structure elements in the first microsecond. The data obtained on the folding of the villin headpiece and lambda repressor will be used to propose mutants that will then be experimentally tested, to verify the observed folding pathway. A 10 microsecond simulation of the WW domain, along with further microsecond trajectories, showed this beta sheet protein not to fold yet properly in the simulations [14]. The data obtained will be used to improve the simulation methods, in particular, the force field employed.

BTA UNIT: T

TITLE: Acceleration of Molecular Modeling Applications with Graphics Processors

KEYWORDS: general-purpose graphics processor computing, molecular modeling software

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ABSTRACT: Over the past several years, the hardware and software architecture of graphics processing units (GPUs) have evolved to the point that they can now be used for general purpose scientific computations. State-of-the-art graphics processors include hundreds of individual arithmetic units that can perform up to 500 billion floating point operations per second, a level of performance far above that available with current generation CPU cores. The Resource has implemented several GPU-accelerated computational kernels for key molecular modeling tasks which achieve performance levels of ten to one hundred times that of traditional CPU implementations (http://www.ks.uiuc.edu/Research/gpu/).

The Resource has developed a new ion placement tool that uses multiple GPUs to accelerate the most computationally demanding parts of the calculation, namely the computation of the electrostatic field surrounding the simulated structure. As reported in [2], the performance gain attributed to the use of the GPUs yielded speedups of up to one hundred or more relative to state-of-the-art CPUs. The electrostatic field calculation was subsequently improved further as reported in [4], and incorporated into VMD, the molecular visualization and analysis package developed by the Resource [64].

GPU acceleration techniques have also recently been applied to NAMD, the parallel molecular dynamics package developed by the Resource. In molecular dynamics simulations, the majority of computation is typically focused on evaluation of forces between atoms that are not chemically bonded. As reported in [2], the use of GPUs has been shown to accelerate this calculation by a factor of ten over state-of-the-art CPUs.

The Resource recently developed a tool for performing simulations of fluorescence microphotolysis for calculation of diffusion coefficients of fluorescent molecules. Analysis of experimental data requires the solution of a diffusion-reaction equation (a partial differential equation in time and 2D or 3D space). As reported in [7], a GPU accelerated implementation of this computational kernel yielded performance twelve times faster than a CPU, bringing the computation time for a simulation down to 38 seconds.

BTA UNIT: C

TITLE: Gating of a Mechanosensitive Channel

KEYWORDS: mechanosensitive (MS) channel, ion channel, molecular dynamics, electron paramagnetic resonance (EPR)

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ABSTRACT: Mechanosensitive channels (http://www.ks.uiuc.edu/Research/MscSchannel) are ubiquitous membrane proteins involved in many biologically relevant processes such as cardiovascular regulation, touch sensation, hearing, and cell volume regulation [15,65–67]. This class of membrane proteins serves as molecular switches, opening and closing in response to stress conveyed through other proteinaceous structures of the cell or the cellular membrane itself [15,66]. In bacteria, mechanosensitive (MS) channels are thought to act as safety valves preventing the cell from bursting upon osmotic shock [18, 68].

Crystal structures of two bacterial MS channels have been solved: the MS channel of large conductance (MscL) in closed form from M. tuberculosis [23] and the MS channel of small conductance (MscS) in a putative open form from E. coli [24].

The X-ray crystal structure of MscS, obtained in a detergent solution at 3.9 Angstrom resolution and missing part of the N-terminal domain, depicts a heptameric channel in an open conformation. Whether the MscS crystal structure represents the fully open conformation of the channel with a conductance of 1 nano-Siemens (as determined through patch-clamp experiments) continues to be debated [24, 25, 30–32, 69–73]. Moreover, two different closed conformations of MscS have been proposed [30, 70], and the voltage-dependence of MscS activation and inactivation remains controversial [25, 32, 68, 74–76]. How the channel dynamically transitions between closed and open conformations is also undetermined [25, 30, 70, 76–78].

Following three previous studies on the transport and gating properties of MscS [30–32], Resource scientists and collaborators have now focused on the refinement of models of its closed and open conformations. The refinement is carried out using data obtained from electron paramagnetic resonance (EPR) experiments performed by Resource collaborator, E. Perozo. These experimental data have been used to guide molecular dynamics simulations, resulting in a model for the closed conformation of MscS that includes the previously missing N-terminal domain [29]. More recent experiments by Resource collaborator E. Perozo have characterized the open state of MscS in situ. The new EPR data have been used to obtain a three-dimensional model for the open conformation of MscS (V. Vasquez, M. Sotomayor, J. Cordero-Morales, K. Schulten, E. Perozo, submitted). The resulting model has been validated through extensive simulations using the Resource software package NAMD. The model is also being used to test whether glutamate, a known osmoprotectant in bacteria, can be passively transported or filtered out by MscS's transmembrane and cytoplasmic domains.

BTA UNIT: T

TITLE: Scalable Molecular Dynamics Software NAMD

KEYWORDS: molecular dynamics simulation, high-performance computing, parallel programming

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ABSTRACT: NAMD (Nanoscale Molecular Dynamics, http://www.ks.uiuc.edu/Research/namd/) is a parallel molecular dynamics code designed for high performance simulation of large biomolecular systems [10, 11]. NAMD employs the prioritized message-driven execution capabilities of the Charm++/Converse parallel runtime system (http://charm.cs.uiuc.edu/), allowing excellent parallel scaling on both massively parallel supercomputers and commodity workstation clusters. NAMD is distributed free of charge to over 25,000 registered users as both source code and convenient precompiled binaries. 5000 users have downloaded multiple releases. NAMD 2.6 was released in August 2006 and has been downloaded by over 10,200 users, 1800 of whom are NIH-funded.

NAMD 2.7 will be released in the fall of 2008. This release will incorporate significant parallel scaling enhancements, including a two-dimensional decomposition of the particle-mesh Ewald method, improved message prioritization, optimized communication for the Blue Gene/L toroidal network, and a new topology-aware load balancer. These enhancements have enabled a recent ten-microsecond simulation of a fast-folding protein [14]. A new compressed molecular data structure allows very large simulations to be run on platforms with limited memory per node. New simulation features in development include coarse-grained models, both fluctuating charge and Drude polarization models, and interface to quantum chemistry codes for QM/MM simulations. The release will also include preliminary support for GPU acceleration based on the CUDA technology from NVIDIA [2].

Large InfiniBand clusters with Intel or Opteron x86-64 processors now dominate high performance computing resources. The introduction of the 9600-core Abe cluster at the NSF center NCSA in May 2007 was followed in December 2007 by the 500-teraflop/s, 63,000-core Ranger cluster at the Texas Advanced Computing Center (TACC). The Resource was granted early friendly-user access to both machines, allowing NAMD to be quickly ported and used for production runs. In order to further improve scaling on these and future clusters, the Resource is experimenting with a direct InfiniBand implementation of Charm++ (bypassing MPI for communication) and multithreaded shared-memory parallelism within a node. NAMD has been independently ported to two new high-end platforms, the IBM BlueGene/P at Argonne and the Cray XT4 at ORNL with the Cray Linux Environment (replacing the Catamount kernel used on the XT3), as well as to the ultra-low-power SiCortex machines.

BTA UNIT: T

TITLE: NAMD-Lite and Molecular Simulation Methods Development

KEYWORDS: molecular dynamics simulation, methods development

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ABSTRACT: NAMD-Lite (http://www.ks.uiuc.edu/Development/MDTools/namdlite/) is a rapid prototyping framework for developing simulation methods for biomolecules, consisting of sequential C language code with a modular design. The intention is to separate the development of methods from the additional complication due to parallel implementation, providing a simpler way to test new tools. The source code is distributed under the University of Illinois/NCSA Open Source License to allow scientists complete freedom to use and modify the code.

NAMD-Lite has assisted in the Resource's effort to accelerate computation using GPUs (graphics processing units). The NAMD-Lite implementation of the multilevel summation method that offers fast electrostatic evaluation for both periodic and nonperiodic boundary conditions [79, 80] was used to speed up the calculation of electrostatic potential maps. GPU acceleration of the short-range part of multilevel summation [2] has been applied to ionization of a molecular system and calculation of time-averaged potentials. The past effort has contributed code to the Cionize plugin of VMD (http://www.ks.uiuc.edu/Research/vmd/). Ongoing efforts include GPU acceleration of the long-range part of multilevel summation, along with a distributed memory parallelization for incorporation into NAMD (http://www.ks.uiuc.edu/Research/namd/).

The Resource has implemented models for polarizable force fields in NAMD-Lite. Polarizable force fields improve accuracy of biomolecular simulation by modeling electron density response to an electric field. The Drude oscillator implementation in NAMD-Lite has been extended to include polarizable ions solvated using a five-point polarizable water model [81]. Work is underway to validate the use of Langevin thermostats for low-temperature simulation of the Drude oscillators, which will provide superior parallel scalability over previously investigated methods [82]. Development of the Drude polarizable force field model in NAMD-Lite will be followed by its implementation in NAMD. The Resource is also implementing the fluctuating charge model for polarization [83, 84] in collaboration with Brooks's NIH Resource Center for Multiscale Modeling Tools in Structural Biology. Ongoing efforts include the addition of a four-point fluctuating charge water model into NAMD, to be followed by more general support for fluctuating charge polarization.

The NAMD-Lite framework is also being used to develop the NLEnergy plugin to VMD that performs energy and force evaluations on VMD atom selections. The capabilities of NLEnergy will be used by the Paratool plugin currently being developed for force field parameterization. The internal data storage and management for NAMD-Lite has been modified to permit fast updates to the force field parameters and topological structure of the molecular system, a key feature to make it

efficient for Paratool.

Advanced simulation methods to study nanopore technology for sequencing DNA [85, 86] are also being developed in NAMD-Lite. This nanopore technology includes semiconductor devices, which have traditionally not been part of biomolecular simulations. The needed simulation methods integrate continuum electrostatics models, which accurately describe semiconductor materials, with molecular dynamics (MD) simulations of biomolecules. The response of a semiconductor capacitor in the presence of DNA will be computed by a continuum solver from previous MD time steps. The continuum solver will update a potential energy grid that exerts an external force back onto the molecular system, modeling the interaction between the DNA and the semiconductor. With the successful development and testing of a combined MD/continuum electrostatics protocol in NAMD-Lite, the method will be parallelized and implemented into NAMD.

BTA UNIT: C

TITLE: Assembly of High-Density Lipoproteins

KEYWORDS: apolipoproteins, Nanodisc, HDL, apo A-I

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ABSTRACT: High-density lipoproteins (HDL) (http://www.ks.uiuc.edu/Research/Lipoproteins/) are protein-lipid assemblies involved in the transport of cholesterol from peripheral tissues to the liver for degradation. HDL is often called "good cholesterol" due to its role in removing excess cholesterol from tissues and blood vessels. Lower levels of HDL have been implicated in an increased risk of coronary heart disease. The production, transformation, and degradation of HDL is regulated by the reverse cholesterol transport pathway. Apolipoprotein A-I (apo A-I), the primary protein component of HDL, initially forms lipid-free/poor HDL particles. The incorporation of cholesterol and lipids into lipid-free/poor HDL particles causes a structural change, forming discoidal lipoprotein particles. Continued efflux of cholesterol and lipids as well as the esterification of cholesterol results in the transformation of the discoidal particles into mature spherical particles, which transport the cholesterol to the liver [87].

Two X-ray crystal structures of lipid-free apo A-I have been determined [88, 89]; however, the structure of apo A-I bound to lipid, in either the discoidal or spherical HDL forms, remains unknown. Since natural HDL particles are heterogeneous in size and composition, it has been impossible to obtain consistent structural data on them [90]. However, reconstituted HDL (rHDL), in which purified (and often truncated) apo A-I is used to form HDL particles, can be made into homogeneous particles. Nanodiscs are an engineered rHDL device being developed by Resource collaborator S. Sligar (UIUC), which can be self-assembled using a precise set of optimized conditions to form discoidal protein-lipid particles with homogeneous size and composition [91]. The Resource utilizes these homogeneous and well-characterized nanodisc particles [92, 93] in molecular dynamics studies [94, 95].

Because the assembly and structural transitions of nanodiscs and HDL occur on timescales longer than those accessible using all-atom MD, a coarse-grained molecular dynamics model has been developed and applied to study this system [5,95–100]. Recent simulations on timescales of 1-10 microseconds have revealed the full assembly path of nanodiscs starting from randomized lipid-protein-water mixtures,and provided final structures for discoidal HDL particles in agreement with small-angle X-ray scattering (SAXS) results [96,97]. In addition, simulations of nanodiscs in the presence of varying amounts of the detergent cholate illustrated the stages involved in HDL assembly and disassembly in the presence of detergent, an important step during reconstitution of HDL particles [98]; again, close agreement was found with SAXS experiments.

BTA UNIT: C

TITLE: Single Molecule Electrical Recording with Nanopore Device

KEYWORDS: nanopore, DNA sequencing, genotyping, human genome, force spectroscopy, silicon, silica, ionic conduction, restriction enzyme

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ABSTRACT: Nanopores are small pores with nanometer-scale radii. They are found in nature, such as the proteinaceous alpha-hemolysin pore [101], but can also be artificially manufactured, as in the case of silicon-based nanopores [102]. When immersed in aqueous solution and with an applied voltage, nanopores can be used to study the translocation of charged species, such as ions or nucleic acids. A promising application of nanopores is DNA sequencing [103]. As DNA translocates through the nanopore, it produces electrical signals characteristic of the sequence and length of the DNA strand. The Resource is working in close collaboration with electrical engineers (Gregory Timp and Jean-Pierre Leburton) to understand the physics and improve the resolution of synthetic nanopores. Atomic-scale modeling was carried out in the following directions: (i) genotyping of DNA with nanopores; (ii) stretching/unzipping DNA hairpins with a nanopore; (iii) sensing DNA sequence with a nanopore capacitor; (iv) developing new computational tools to speed up DNA translocation and (v) modeling of ionic current through silica nanopores (http://www.ks.uiuc.edu/Research/nanopore/).

Another use of nanopores is as electrical tweezers. Such use has been realized to study restriction enzymes, which selectively bind to specific DNA sequences. The restriction enzyme EcoRI was investigated [104], driving the EcoRI-DNA complex by means of applied voltage through a silicon nitride nanopore narrow enough to allow the passage of the DNA, but not passage of the enzyme. Experiments showed that there is a voltage threshold at which the EcoRI separates from the DNA, the threshold depending on the DNA sequence. Molecular dynamic (MD) simulations revealed that the threshold is associated with a nanoNewton force required to rupture the EcoRI-DNA complex. A single mutation in the recognition site for the restriction enzyme can be detected as a change in the threshold voltage.

The electromechanical properties of DNA can be studied by using an electric field, which drives a single hairpin molecules through a synthetic nanopore. Similar to the enzyme-DNA work describe above, a threshold voltage was observed for translocation of the hairpin through the pore, which depends on the diameter and the secondary structure of the DNA [105]. The threshold for a diameter from 1.5 to 2.3 nm is higher than 1.5 V and corresponds to the force required to stretch the stem of the hairpin, according to MD simulations. On the other hand, for nanopore diameters from 1.0 to 1.5 nm, the threshold voltage is lower than 0.5 V because the stem unzips with a lower force than required for stretching. These results suggest that a synthetic nanopore can be used as a molecular gate to distinguish the secondary structures in DNA.

The Resource has also investigated the feasibility of sequencing DNA using an electric field in a nanopore that periodically alternates in time and suggested a

strategy for sequencing DNA with single-base resolution [106]. MD simulations revealed that back-and-forth motion of DNA strands through a 1-nm diameter pore exhibits sequence-specific hysteresis due to the tilting of DNA bases in the pore constriction. Such hysteresis is sequence specific and may produce detectable changes in the electrostatic potential at the electrodes of the nanopore capacitor and a sequence-specific drift of the DNA strand.

Many applications of nanopores are based on measuring the changes in the ionic current. Therefore, understanding the ion dynamics through nanopores is desirable. The Resource has been studying the rectification of ionic current on nanopores, i.e., where ionic current measurements are higher for one voltage polarity than for the same voltage with opposite polarity, producing an asymmetric current-voltage (I-V) curve. Using MD simulations, the Resource performed a systematic study of the KCl conductance in silica nanopores, using a variety of silica nanopore and simulation conditions. The results indicate that ion-binding sites at the silica surfaces affect the ionic concentration and electrostatic potential inside the nanopore [107].

BTA UNIT: C

TITLE: Single-walled carbon nanotubes as optical sensors

KEYWORDS: Single-walled carbon nanotube (SWNT), excitons, length-dependent dynamics, SWNT-biomolecule interactions, relative quantum yield, photoluminescence lifetimes, diffusion

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ABSTRACT: ABSTRACT

Optical properties of single-walled carbon nanotubes (SWNTs) are generating a lot of interest because of their potential use as optical sensors, especially in biological environments. SWNTs fluoresce in the near-infrared region and excitons are understood to be responsible for the optical transitions observed [108–110]. The spectra of SWNTs have been shown to be very sensitive to changes in their biological environment [111–113]. The Resource has previously built efficient force fields to study the interaction between SWNTs and biomolecules using molecular dynamics (MD) simulations [114–119](http://www.ks.uiuc.edu/Research/nanotube/). Apart from studying such systems through MD simulations, the Resource has also started developing both phenomenological and microscopic models to study the optical properties of SWNTs.

Experiments conducted in the Strano group (MIT) demonstrated that as the SWNTs were made shorter, their quantum efficiencies dropped nonlinearly [120]. This phenomenon has many implications for optical sensor applications as it suggests that

there are limits to reducing the size of SWNTs used as sensors. To understand what the underlying limiting processes are, the Resource has developed a model involving diffusion of excitons along the length of the nanotube and quenching (due to edge states) at the nanotube ends. The phenomenological model fit very well with the Raman spectroscopy data of different length fractions (in the range of 100 to 500 nm) of SWNTs from the Strano lab. From the fit, a value for the diffusion coefficient of excitons was obtained [121], which was found to be in close agreement with values reported from other experiments in the literature [122]. These findings suggest that the quenching at the ends of the SWNTs is both rapid and very large. Almost all excitons that reached the ends seem to get quenched. It is very important to consider quenching due to edge states when designing SWNT-based optical sensors.

From the diffusion-based model, the length dependence of the photoluminescence lifetimes of excitons in these tubes was also extracted. Recent data from the Strano and Hertel (Vanderbilt University) groups have shown that the quantum efficiencies of SWNTs saturate at about 3 percent for length fractions larger than a micrometer. The diffusive model was extended by introducing a nonradiative decay parameter and was found to fit very well with independent spectral measurements from the Hertel and Strano labs. The Hertel lab is now making high-precision lifetime measurements on these SWNT samples, which will shed more light on the temporal dynamics of excitons in SWNTs.

Our results seem to indicate that very short SWNTs are not optimal for use as optical sensors due to their poor quantum efficiencies. In addition to its previously stated goals of understanding SWNT-biomolecule interactions through MD simulations, another goal of the Resource is to understand the limiting processes involved in making SWNTs shorter in optical sensor or imaging applications. In collaboration with the Strano and Hertel groups, the Resource aims to model, both phenomenologically and at the microscopic level, the length-dependent dynamics of excitons in SWNTs.

BTA UNIT: C

TITLE: Simulating a Bacterial Organelle

KEYWORDS: photosynthesis, atomic force microscopy, purple bacteria, bioenergetics, energy transfer, quantum biology, light harvesting complex, reaction center, Rhodobacter sphaeroides, spherical membrane, membrane curvature, bacteriochlorophyll, PSU, LH1, LH2, BchI, AFM

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ABSTRACT: Photosynthesis is the bioenergetic process by which the majority of Earth's biosphere derives energy from sunlight. This efficient sub-cellular process depends on the complex organization of the photosynthetic unit (PSU) at multiple scales spanning from sub-nanoscale atomic processes to macroscale multi-protein and lipid assemblies that are integral components of PSU organelles. One such organelle found in the purple bacterium Rhodobacter sphaeroides is the chromatophore, a 70 nm wide bulbous invagination of the inner membrane containing a total of approximately 200 proteins, 5,000 chlorophylls, and 1,700 carotenoids that permit efficient photosynthesis. These 200 chromatophore proteins consist of several multi-protein complexes, including 20 photosynthetic reaction centers (RC) [123, 124], 20 light harvesting complexes 1 (LH1) [125, 126], 150 light harvesting complexes 2 (LH2) [127, 128], five bc1 complexes (bc1) [129] and cytochrome c2s [130], and usually one ATP synthase [131]. Involving 70 million atoms, continued development of coarse-graining tools and the extension of VMD and NAMD capabilities will be necessary to accommodate such a large system computationally. Representing one of the first simulations at the near-cellular level, the chromatophore system will also strenuously test the scalability of VMD and NAMD while providing unique opportunities to investigate one of the most fundamental processes necessary for life on Earth, namely the conversion of light into bioenergy.

Modeling the collective behavior of a PSU requires the knowledge of how its 200 proteins interact and assemble into a spherical chromatophore organelle. Mutant studies on Rhodobacter sphaeroides suggest that LH2 is largely responsible for the spherical geometry of the chromatophore, while in LH2-deficient mutants, LH1 dimers drive the formation of tubular chromatophores [132–135]. The hypothesis of the bidirectional curvature effect of LH2 and the unidirectional curvature effect of LH1 is yet to be verified. Also, the curvature properties of bc1 might offer insight on its location within the chromatophore vesicle.

To investigate curvature properties of LH1, LH2 and bc1, separate all-atom models of each protein embedded in membrane patches have been developed, and equilibration simulations have been carried out for all three systems [136]. For the LH2 system, seven LH2s arranged in a tight hexagonal array were placed in a lipid membrane patch, and equilibration of this system showed that each LH2 tilts away from its neighbors to produce a net curvature [136]. This curvature appears to

be driven by a combination of physical packing and electrostatic repulsion, and is strongly dependent on the packing density of the LH2s. For the LH1 system, it was observed that the LH1 dimer develops a bend at the dimerization interface during equilibration [136]. Its bent shape then drives the surrounding lipids to conform to a curved state, resulting in a unidirectional curvature [136]. Such dimer bending has also been observed experimentally by collaborators of the Resource. Unlike LH1 and LH2, the membrane-embedded bc1 system did not actively induce curvature, whether placed singly or in pairs [136]. However it still remains to be tested whether bc1 prefers a certain membrane curvature state, which may resolve the placement of bc1 within the chromatophore bulb. Together these simulations illustrate, at an unprecedented atomic resolution, that the chromatophore proteins are capable of inducing membrane curvature, and that aggregation of these proteins may drive the formation of the chromatophore bulb. With an understanding of single-protein curvature properties, construction of a complete, membrane-bound functional chromatophore is now possible and is underway.

This subproject is carried out mainly as a driving force for the structural systems biology core of the Resource. One the one hand, the needed calculations are extremely demanding, requiring multi-million atom simulations. One the other hand, the subproject is a long-term effort towards whole cell modeling, requiring modeling methodologies on many scales, from the electronic level, to the atomic level, to various coarse-grained levels, and preparing the ground work for future collaborations.

BTA UNIT: C

TITLE: Structural Analysis of the Ribosome

KEYWORDS: ribosome, multiscale, translation, RNA, molecular dynamics, flexible fitting, cryo-electron microscopy

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ABSTRACT: The ribosome [35] is a cellular machine that synthesizes proteins based on genetic instructions. The ribosome moves along the mRNA, catches tRNAs, facilitates the pairing between codons and anticodons, and catalyzes the formation of peptide bonds between amino acids. The bacterial ribosome is an important target of antibiotics; indeed, 50% of all research on antibiotics is focused on the ribosome. Currently the most successful approaches to image ribosomes are cryo-electron microscopy (cryo-EM) [37] and X-ray crystallography [38]. Cryo-EM offers insights

into the function of the ribosome by providing snapshots of different functional states, currently at a resolution of 7 Angstroms, while X-ray crystallography provides atomic-scale structural information [38] for single or undefined functional states. These and other experiments show that the ribosome consists of two subunits, the small subunit being responsible for codon-anticodon recognition, and the large subunit for catalyzing peptide bond formation. The whole translation machinery consists of ribosomal RNAs, about 50 ribosomal proteins, tRNAs, mRNA, ions, and additional protein factors.

In order to investigate ribosomal function at much needed atomic detail, the Resource developed in close collaboration with J. Frank (Columbia U.) a novel method to fit atomic structures into cryo-EM density maps, thus obtaining atomic-resolution models of the ribosome in different functional states [6]. The method, molecular dynamics flexible fitting (MDFF; http://www.ks.uiuc.edu/Research/mdff), incorporates the EM map as a potential to actively drive the atomic model into the density, effectively sampling the structural variability present in the experimental map. During the fitting process, the atomic structure and the molecular dynamics force field determine the structural flexibility, while keeping the model stereochemically correct. These features obviate the need for user-defined flexibility and post-fitting refinement, the latter often leading to deviations from the map. Moreover, because MDFF does not rely on global optimization criteria, and since MDFF employs the molecular dynamics simulation software NAMD, the method scales well with system size, permitting its application to large, asymmetric macromolecular assemblies like the ribosome. Resource scientists jointly with the Frank laboratory have obtained atomic structures for twelve different conformational states of the ribosome, which will be used to study the conformational changes that take place during the decoding process.

BTA UNIT: C

TITLE: The Protein-Conducting Channel

KEYWORDS: translocon, SecY, translocation, protein channel

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ABSTRACT: The protein-conducting channel, more specifically known as the translocon (http://www.ks.uiuc.edu/Research/translocon/) or Sec complex, is an evolutionarily ancient protein complex that helps proteins cross or integrate into membranes (depending on whether they are soluble or membrane proteins). Present in all branches of life, the Sec complex is found in the cytoplasmic membrane in bacteria and archaea and in the membrane of the endoplasmic reticulum in eukaryotes. A passive channel, the Sec complex partners with other proteins that drive translocation of an unfolded polypeptide through the channel. In co-translational translocation, a common mode of translocation, this partner is the ribosome which feeds the nascent protein through the channel as it is synthesized. As a key step in protein targeting, translocation can be a deciding factor in the fate of proteins and even the cell as a whole. For example, poor recognition of the prion protein (PrP) leads to its abnormal aggregation and ultimately to lethal levels in the cell [137]. However, being able to enhance recognition and passage across the membrane could increase yields for artificially created proteins such as insulin [138]. In 2004, the Resource's collaborator, Tom Rapoport, released the first high resolution structure of the translocon. Obtained from Methanococcus jannaschii, this heterotrimeric membrane protein complex was resolved to 3.5 Angstroms. Based on this structure, specific details of translocation began to emerge. Observed structural elements were proposed to have specific functions, such as a constrictive pore ring and a plug blocking the exit of the channel. It was also proposed that a singular monomer within a dimeric or tetrameric complex serves as the active channel, leaving the

role of oligomerization in question. Two dimeric forms of the channel with different functional behavior have been proposed (a 'back-to-back' and a 'front-to-front' dimer) although which is the in vivo state is unknown.

The Resource's investigations previously illustrated both how proteins are translocated across the membrane and how SecY opens laterally to the membrane [139, 140]. More recently, Resource researchers have characterized two mutants in which half or all of the plug is deleted, both crystallized by Tom Rapoport [141]. The structures revealed that new, less stable plugs had formed from the remaining residues. Although the pore ring was still closed in the structures, electrophysiology experiments indicated that the channels are permeable to water and ions [142]. Extensive simulations of the 100,000-atom system totaling more than 0.25 microseconds have illustrated why the mutants permit conduction while the native state does not [143]. It was found that the pore ring in the mutants fluctuates between open and closed states, permitting intermittent water permeation, due to decreased interactions with the new plugs. In a novel simulation in which the plug was assumed to be transparent to water, it was found that the plug serves primarily to stabilize the pore ring, rather than acting only as a steric barrier to the flow of water and ions. The results expand on the model for gating of the channel, explaining how destabilization of the plug can lead to channel opening.

Current efforts have also taken advantage of the Resource's work on the ribosome as well as on the Resource's molecular dynamics flexible fitting method [6]. Employing this method, fitting of atomic structures of the ribosome and translocon was performed using a recently obtained cryo-EM map of a ribosome bound to a monomer of the translocon [144]. After fitting, addition of water, membrane, and ions resulted in a system composed of 2.7 million atoms. Simulation of this system requires use of the latest memory optimized version of NAMD. Preliminary results, based on 15 ns of simulation, indicate that the ribosome destabilizes portions of the translocon, including the plug, preparing the channel for translocation.

BTA UNIT: C

TITLE: Developing Tools for Structural Systems Biology

KEYWORDS: structural systems biology, ribosome, coarse grain, system building

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ABSTRACT: The very nature of living systems lies in the harmonious hierarchical assembly, regulation, and function of their biomolecular building blocks. In the past, the Resource has focused its research and modeling tool development mainly on the building blocks, but is now shifting its attention to the assembly level, developing modeling tools for structural systems biology. This shift has required existing tools to become more efficient in order to handle much larger structures, more automated in order to assist the modeler in building and analyzing models, and more comprehensive in order to address the modelers' wider range of tasks.

Significant progress has been made in the past year on the "Biomolecular Modeling Suite", which is a wide collection of modeling tools that have been incorporated into VMD, thus making them available to VMD's large user community. The Shape-Based Coarse Graining (SBCG) tool has been improved to make it even more useful for scientists modeling large CG systems. The Timeline tool has been enhanced to work with arbitrary selections within VMD (not just residues) and several tools needed for docking, including tools for restraining the secondary structure of proteins or nucleic acids in NAMD simulations, have been added.

QMtool and Paratool are user interfaces in VMD for quantum chemistry simulations and force field parameterization. While prior versions of QMtool supported the widespread commercial quantum chemistry package Gaussian03 [145], the current version of QMtool offers basic support for simulations using GAMESS [146], a popular free program. A graphical user interface has been added for selecting the simulation parameters and for automatic generation of simulation input files with the coordinates in the appropriate format. Furthermore, Paratool and QMtool are currently undergoing a process of modularization and redesign in order to enable their use as both graphical frontends for the user and as command line tools to be called by other plugins.

Molefacture has evolved into a powerful molecular editor allowing one to build arbitrary molecules using a built-in fragment library. Polypeptides and nucleic acid strands can easily be generated with Molefacture's protein and nucleic acid builder, respectively. Internal coordinates like bond lengths or dihedral angles can now be edited interactively. Finally, Molefacture can now automatically assign atom and bond types using Antechamber [147].

BTA UNIT: T

TITLE: VMD, a Program for Model Building, Structure Analyzing, and Sequence Analyzing

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ABSTRACT: VMD [64] is a molecular visualization program that provides interactive biomolecular display as well as a wide range of model building and analysis capabilities. VMD incorporates scripting and plugin interfaces for user-extensibility and automation of complex tasks.
(http://www.ks.uiuc.edu/Research/vmd/)

VMD runs on all major operating systems and supports computers ranging from laptops to supercomputers. VMD utilizes advanced hardware technologies including stereoscopic displays, six-degree-of-freedom input devices with haptic feedback, multiprocessor and clustered rendering systems, OpenGL, programmable shading, 64-bit addressing, multi-core processors, and GPU-accelerated computation.

In the past year, VMD has been improved through many new features, has been ported to new platforms, and has been tuned to provide higher compuational and graphical performance. VMD has been ported to the 64-bit PowerPC architecture, in support of the "Big Red" cluster at Indiana University, one of the NSF Teragrid supercomputers. VMD now makes more extensive use of GPU-accelerated algorithms to achieve high performance for computationally demanding tasks such as calculation of electrostatic fields surrounding molecular structures [2]. VMD now supports improved analysis and display of carbohydrate structures, implementing an improved version of the techniques described in [1]. Several key VMD analysis and visualization features now operate directly, i.e., without the need for preprocessing, on molecular models that use periodic boundary conditions. The accuracy of RMS structure alignment has been improved with the use of tighter error tolerance. Several new user-defined time varying data fields have been added to VMD to support development of sophisticated analysis scripts with improved performance. The structure analysis routines in VMD have been updated to accommodate new atom type identification strings found in the public protein databank. New and updated plugins provide additional molecular and volumetric file format support. VMD has recently been updated with support for version 2.5 of the Python scripting language, and version 8.5 of the Tcl scripting language.

Over 30,000 users have registered for VMD 1.8.6 since it was released on April 7, 2007. An updated set of VMD 1.8.6 plugins was released on September 21, 2007, primarily adding support for new file formats and addressing bugs reported by the user community.

Ongoing VMD developments include improved tools for structure building, multiple sequence alignment, simulation analysis, improved graphical representations, improved capabilities for operating on volumetric data, and increased use of parallel

processing for performance improvements based on multicore and GPU-accelerated algorithms. The next release of VMD is planned for the summer of 2008.

Resource Summary

BTA unit: (T)

NUMBER PUBLISHED -

Books: **??** Papers: **??** Abstracts: **??**

NUMBER IN PRESS -

Books: **??** Papers: **??** Abstracts: **??**

PUBLISHED:

Books:

Papers:

Abstracts:

IN PRESS:

Books:

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BTA unit: (C)

NUMBER PUBLISHED -

Books: **??** Papers: **??** Abstracts: **??**

NUMBER IN PRESS -

Books: **??** Papers: **??** Abstracts: **??**

PUBLISHED:

Books:

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BTA unit: (S)

NUMBER PUBLISHED -

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

NUMBER IN PRESS -

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

PUBLISHED:

Books:

None.

Papers:

None.

Abstracts:

None.

IN PRESS:

Books:

None.

Papers:

None.

Abstracts:

Software Releases

BTA unit: (D)

NUMBER PUBLISHED -

Books: **??** Papers: **??** Abstracts: **??**

NUMBER IN PRESS -

Books: **??** Papers: **??** Abstracts: **??**

PUBLISHED:

Books:

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The Resource submitted in fall 2006 its 5-year renewal application, and had in spring 2007 the site visit associated with the review process. Now in the first year of the renewed funding, the Resource is currently organizing its first Advisory Board meeting for July 28, 2008. Those to be invited to serve on the Advisory Board include:

- Dr. Angel Garcia, Senior Constellation Chaired Professor in Biocomputation and Bioinformatics, Rensselaer Polytechnic Institute
- Dr. Angela Gronenborn, Chief of Structural Biology, Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health
- Dr. Richard Pastor, Senior Investigator, Department of Health and Human Services, National Institutes of Health
- Dr. Dave Thirumalai, Professor, College of Computer, Mathematical and Physical Sciences, Institute for Physical Science and Technology, University of Maryland at College Park
- Dr. Michael Heath, Director of Computational Science and Engineering, University of Illinois at Urbana-Champaign

Administration

Organization

The organization and operation of the Resource supports development and distribution of software, collaborations, user service, and interactions between researchers and developers. Software development, both of current and planned applications, is the central responsibility of assigned developers, with input and assistance from other members of the Resource. Software distribution occurs via the Resource web site, with application web sites managed by the software developers. Server hardware underlying the web site is maintained by the Resource's system administration team. Collaborations with external scientists, where Resource graduate students, postdoctoral associates, and faculty work with outside researchers on projects that require new methodological solutions, benefit from and provide direction to software development.

The Resource's many service, training, and dissemination activities involve all members of the Resource, *e.g.*, hosting external scientists in the visitor center, or providing members of the biomedical community access to Resource computing facilities. Interactions stemming from collaborations, other sources of input from external scientists, and internal contacts between Resource scientists and developers, as supported by administrative structures, produce a dynamic environment that fosters both research and development. Activities of the Resource are supported by both external and internal organizational structures.

External Structures. The Resource resides within the Beckman Institute for Advanced Science and Technology*, at the University of Illinois at Urbana-Champaign (UIUC)†, one of three campuses of the University of Illinois system. The mission of the Beckman Institute is to foster basic, interdisciplinary research as focused around three reseach initiatives: biological intelligence, human-computer intelligent interaction, and molecular and electronic nanostructures. Organizationally, the Resource belongs to the molecular and electronic nanostructures research initiative, where the emphasis is on developing a fundamental understanding of chemical and physical processes involving structures on the nanometer scale. The Resource is involved in close collaborative projects with other groups that are part of this research initiative, mainly in the area of biotechnology.

Administratively, the Director of the Beckman Institute reports to the campus Provost and Vice Chancellor for Academic Affairs. Resource members Drs. Schulten, Luthey-Schulten, Kalé, Tajkhorshid, and Aksimentiev all have faculty appointments at the Beckman Institute. Other contacts with major campus units come through the UIUC faculty positions of primary Resourceinvestigators. Drs. Schulten and Aksimentiev have appointments in the Department of Physics; Drs. Schulten, Luthey-Schulten and Tajkhorshid

*`http://www.beckman.uiuc.edu/`

†`http://www.uiuc.edu/`

have affiliations with the Center for Biophysics and Computational Biology (a unit of the Department of Molecular and Cellular Biology); Dr. Luthey-Schulten has an appointments in the Department of Chemistry; Dr. Tajkhorshid has an appointment in the Departments of Pharmacology and Biochemistry; Dr. Kalé has an appointment in the Department of Computer Science.

Internal Structures. Internally, the Resource is led by Principal Investigator (PI) Klaus Schulten, and Co-PIs Laxmikant Kalé, Zaida Luthey-Schulten, Emad Tajkhorshid, and Alek Aksimentiev with Dr. Schulten serving as Director and Dr. Tajkhorshid serving as Assistant Director. Guidance, information, and expertise is also provided by the Resource's Advisory Committee. Working under Resource leadership are four software developers, six postdoctoral associates, 20 graduate students, and three administrators.

Three functional internal subunits - technical and administrative support, technological development, and collaborations - carry out Resource operations. The subunit technical and administrative support includes development and maintenance of computing clusters; maintenance of desktop machines and network connections; and, clerical and administrative support, including interfacing with other campus administrative units. Members of the technological development subunit spend the majority of their time developing software for the Resource. Included under the collaborations subunit is work with external scientists, typically involving one or more Resource graduate students or postdoctoral associates, a faculty member, and a member of the technological development unit.

Any given task carried out by the Resource is likely to involve multiple members of any one of the organizational subunits, for example a collaborative project will typically require support from the other two units. All members participate in the administration of the Resource by taking on tasks related to operation of the Resouce, such as assisting in system administration, or contributing to the web site. Resource members also attend regular all-member and subgroup meetings. A highly-developed internal website tracks meetings and provides information and resources in four main categories: administration and service, events and outreach, databases and records, and a catch-all miscellaneous category. For example, meeting agendas and minutes generated by general meetings of all Resource members are kept on the internal site, providing useful reference documentation for decisions on any number of topics addressed during the meetings.

Two committees, the Collaboration Selection Committee and the Software Features Committee, support the missions of the Resource. The Collaboration Selection Committee, comprised of the PI and Co-PIs of the Resource, and meeting about four times a year, decides which collaborations should be pursued based on suggestions from a number of sources - direct requests, suggestions by Resource members, contact at meetings and conferences, and so on. Selection is based on criteria such biomedical relevance, quality/originality of the suggested research, computational demands, and general fit with

Resource goals and structures. The Software Features Committee is comprised of external scientists who are asked to suggest and prioritize new features for each of the major software applications being developed by the Resource, using criteria such as potential benefit of a feature to biomedicine, what benefits can be attributed to a feature, and fit of the proposed features with the overall goals of the Resource software. A new iteration of Software Features Committee input is being developed for the next funding period.

Allocation of Resource Access

Access to the Resource is provided at three general levels: access to Resource software, to software developers/development, and to Resource expertise. Access to Resource developed software - Visual Molecular Dynamics (VMD)*, Nanoscale Molecular Dynamics (NAMD)†, and Biological Collaborative Environment (BioCoRE)‡ - is provided via the Resource's popular web site§. Information on the number of registered users of each application is provided below, along with statistics on use of the web site and counts of external users accessing the Resource's computational facilities. Users have also access to software support by email. Statistics of this widely-used service are also provided below.

Access to Resource development efforts - the opportunity to interact with software developers - is provided via multiple channels. All major software applications provide e-mail contacts and mailing lists. Further, the VMD application web site provides a Public Project via BioCoRE¶, where the user community can exchange tips and information about VMD, and the NAMD web site provides a wiki‖ of user-modifiable web pages on numerous topics. Information describing exchanges with software developers (e.g., the number of emails with developers) is provided below.

Access to Resource expertise is also available via multiple channels. Collaborations, as represented by the subprojects included with this report, represent a long-term access of Resource expertise, and as such are carefully selected by the Resource. Other accesses of Resource expertise include the Resource's visitor program and other training efforts as described in the *Training* section, and indicators of the success of the Resource in reaching the biomedical community (e.g., via publications, news stories, lectures) is provided in the *Dissemination* section.

Access accomplishments by the Resource as related to access/service over the last year include:

- 20,070 additional downloads of VMD
- 4,941 additional downloads of NAMD

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

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

‡http://www.ks.uiuc.edu/Research/biocore/

§http://www.ks.uiuc.edu/

¶http://biocore.ks.uiuc.edu/biocore/biofs/VMD%20(Public)/index.html

‖http://www.ks.uiuc.edu/Research/namd/wiki/

- 807 additional registered users of BioCoRE
- 4,822 VMD emails, 420 NAMD emails, and 316 BioCoRE chats and emails were exchanged in user support
- 2,553 citations of the VMD source paper; 861 citations of the NAMD source papers
- over 390,000 unique visitors to Resource software web site
- 24 seminars organized by the Resource

The Resource is engaged in intensive development efforts and technology transfer. A number of software packages, particularly VMD, NAMD and BioCoRE, as well as a number of smaller programs, are freely distributed. All Resource-developed programs, binaries and source, are available on our web site for easy accessibility, employing a unified distribution mechanism**. The VMD, NAMD and BioCoRE packages are developed, maintained, and distributed by Resource staff. The staff also offers extensive user support and has turned the Resource web site into a leading and a widely recognized distribution resource for biomedical software. In this report we are focusing on the development, distribution and support accomplishments of VMD, NAMD and BioCoRE, over the last year.

Use of VMD, NAMD, and BioCoRE

VMD has 108,835 downloads as of April 2008 (an increase of 20,070 or +23% since March 2007), with 25,661 of those downloads by repeat users (i.e., they have downloaded more than one version of VMD), and 19% of all downloaders indicating NIH funding. The current version of VMD, VMD 1.8.6, has 29,632 downloads since its release in April 2007, with 5,519 or 19% of downloaders indicating they are NIH funded users.

NAMD has 25,197 downloads (as of April 2008) (an increase of 4,941 or +24% since March 2007), of whom 5,049 or 20% are repeat downloaders. 4,257 (17%) of NAMD downloaders are NIH funded. The current version of NAMD, version 2.6 released in August 2006, has 10,205 downloads, with 1,825 or (18%) of downloaders indicating NIH funding.

BioCoRE has 2,746 registered users (an increase of 807, or +42% in the past year), involved in 516 projects (compared to 464 a year ago). A total of 82 projects within BioCoRE have been reported as either fully or partially NIH-funded.

VMD Development and User Support

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

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

VMD Enhancements for 2007-2008 include amongst other features:

- VMD now makes more extensive use of GPU-accelerated algorithms to achieve high performance for computationally demanding tasks, such as calculation of electrostatic fields surrounding molecular structures
- VMD now supports improved analysis for the display of carbohydrate structures, implementing an improved version of recently described techniques [1]
- Accuracy of RMS structure alignment has been improved with the use of tighter error tolerance
- Structure analysis routines in VMD have been updated to accommodate new atom type identification strings found in the public protein databank
- Several new user-defined time varying data fields have been added to VMD to support development of sophisticated analysis scripts with improved performance
- VMD has been updated with support for version 2.5 of the Python scripting language and version 8.5 of the Tcl scripting language, providing greater flexibility for user script development

Scope of VMD User Support:

- 4,822 e-mail exchanges in response to user inquiries sent to the vmd@ks.uiuc.edu e-mail address
- 814 subscribers to the VMD-L mailing list, with 11,711 total postings, and 2,219 postings for the May 2007 - April 2008 period
- Local face-to-face support has been provided

There are currently 456 non-Resource users with access to the VMD source code repository, with 79 such users added in the last year.

Sites with Links to the VMD Site (via Yahoo! site search, April 2008): 3,889 links

NAMD Development and User Support

During the reported period, NAMD enjoyed significant improvements and continued to increase in its number of registered users. The program is widely considered as uniquely satisfying the demand for an effective program on the new generation of teraflop parallel computers.

NAMD Enhancements for 2007-2008 include among other features:

- Two-dimensional decomposition of particle-mesh Ewald.
- Improved message prioritization.
- Optimized communication for the Blue Gene/L toroidal network.
- GPU acceleration based on the CUDA technology from NVIDIA.
- Direct support for InfiniBand networks.
- Multithreaded shared-memory parallelism.
- Compressed molecular data structure for reduced memory-limited machines.
- Ports to Cray Linux Environment, IBM BlueGene/P, and SiCortex.
- Ports to large multicore clusters at NCSA and TACC.

NAMD Availability in Supercomputer Centers:

- Pittsburgh Supercomputing Center
- National Center for Supercomputing Applications
- San Diego Supercomputer Center
- Indiana University
- Texas Advanced Computing Center

Scope of NAMD User Support:

- The NamdWiki user-editable web site contains 49 topical pages, with the ability for users to add their own pages, providing a public whiteboard for sharing NAMD issues, experiences, providing advice, and troubleshooting; sample wiki topics are "NAMD Performance Tuning" and "NAMD at PSC"
- 672 subscribers to the NAMD-L mailing list, with 7,617 total postings, and 1,953 postings for the May 2007 - April 2008 period
- Over 420 emails exchanged with users via the namd@ks.uiuc.edu e-mail address, a number which excludes questions sent to the Charm++ developers or the NAMD and VMD mailing lists
- Local face-to-face support has been provided

There are currently 327 users with access to the NAMD source code repository, with 67 users added in the last year.

Sites with Links to NAMD site (via Yahoo! site search, April 2008): 1,679 links

BioCoRE User Support:

- 62 emails issued to/from biocore@ks.uiuc.edu from April 2007 - March 2008
- 254 chat messages sent to the BioCoRE public help project from April 2007 - March 2008 within BioCoRE itself.

Sites with Links to BioCoRE site (via Yahoo! site search, April 2008): 425 links

Citations of Software Source Papers

All users of Resource software are asked to acknowledge in any journal or other publications the source paper for the software that they used. Searches of online citations databases then provide one means of indicating the use of a software application. Recent citation search results for the VMD, NAMD, and BioCoRE source papers are provided below.

List of papers citing VMD: A literature search in the ISI Web of Science citation database in April 2008 yielded 2,553 published journal articles, papers, or books citing the VMD origin paper [64]. Below are 25 recent citations:

- Gryk, M. R., & Hoch, J. C. (2008). Local knowledge helps determine protein structures. *Proceedings of the National Academy of Sciences of the United States of America*, 105(12), 4533-4534.
- Ma, H., Luo, M. X., & Dai, L. L. (2008). Influences of surfactant and nanoparticle assembly on effective interfacial tensions. *Physical Chemistry Chemical Physics*, 10(16), 2207-2213.
- Kraszewski, S., Yesylevskyy, S. O., Boiteux, C., Ramseyer, C., & Kharkyanen, V. N. (2008). Is the mobility of the pore walls and water molecules in the selectivity filter of KcsA channel functionally important? *Physical Chemistry Chemical Physics*, 10(16), 2249-2255.
- Hanasaki, I., Takahashi, H., Sazaki, G., Nakajima, K., & Kawano, S. (2008). Single-molecule measurements and dynamical simulations of protein molecules near silicon substrates. *Journal of Physics D-Applied Physics*, 41(9).
- Sears, J. S., & Sherrill, C. D. (2008). Assessing the performance of density functional theory for the electronic structure of metal-salens: The 3d(0)-metals. *Journal of Physical Chemistry A*, 112(15), 3466-3477.

- Horta, B. A. C., Cirino, J. J. V., & de Alencastro, R. B. (2008). On the structure, interactions, and dynamics of bound VEGF. *Journal of Molecular Graphics & Modelling*, 26(7), 1091-1103.

- Jacob, C. R., Neugebauer, J., & Visscher, L. (2008). Software news and update a flexible implementation of frozen-density embedding for use in multilevel Simulations. *Journal of Computational Chemistry*, 29(6), 1011-1018.

- Vallejo, D. F. G., Grigera, J. R., & Costabel, M. D. (2008). A hydrophobic loop in acyl-CoA binding protein is functionally important for binding to palmitoyl-coenzyme A: A molecular dynamics study. *International Journal of Biological Macromolecules*, 42(3), 271-277.

- Yogurtcu, O. N., Erdemli, S. B., Nussinov, R., Turkay, M., & Keskin, O. (2008). Restricted mobility of conserved residues in protein-protein interfaces in molecular simulations. *Biophysical Journal*, 94(9), 3475-3485.

- Jeon, J., & Voth, G. A. (2008). Gating of the mechanosensitive channel protein MscL: The interplay of membrane and protein. *Biophysical Journal*, 94(9), 3497-3511.

- Cupp-Vickery, J. R., Igarashi, R. Y., Perez, M., Poland, M., & Meyer, C. R. (2008). Structural analysis of ADP-glucose pyrophosphorylase from the bacterium Agrobacterium tumefaciens. *Biochemistry*, 47(15), 4439-4451.

- Cymes, G. D., & Grosman, C. (2008). Pore-opening mechanism of the nicotinic acetylcholine receptor evinced by proton transfer. *Nature Structural & Molecular Biology*, 15(4), 389-396.

- Akiyama, S., Nohara, A., Ito, K., & Maeda, Y. (2008). Assembly and disassembly dynamics of the cyanobacterial periodosome. *Molecular Cell*, 29(6), 703-716.

- Dalkas, G., Papakyriakou, A., Vlamis-Gardikas, A., & Spyroulias, G. A. (2008). Low molecular weight inhibitors of the protease anthrax lethal factor. *Mini-Reviews in Medicinal Chemistry*, 8(3), 290-306.

- Neyertz, S., & Brown, D. (2008). Molecular dynamics simulations of oxygen transport through a fully atomistic polyimide membrane. *Macromolecules*, 41(7), 2711-2721.

- Song, W., Wei, G. H., Mousseau, N., & Derreumaux, P. (2008). Self-assembly of the beta 2-microglobulin NHVTLSQ peptide using a coarse-grained protein model reveals beta-barrel species. *Journal of Physical Chemistry B*, 112(14), 4410-4418.

- Thode, A. B., Kruse, S. W., Nix, J. C., & Jones, D. N. M. (2008). The role of multiple hydrogen-bonding groups in specific alcohol binding sites in proteins: Insights from structural studies of LUSH. *Journal of Molecular Biology*, 376(5), 1360-1376.

- Cyranski, M. K., Jezierska, A., Klimentowska, P., Panek, J. J., Zukowska, G. Z., & Sporzynski, A. (2008). Structural and spectroscopic properties of an aliphatic boronic acid studied by combination of experimental and theoretical methods. *Journal of Chemical Physics*, 128(12).

- Kindt, P., & Briels, W. J. (2008). The role of entanglements on the stability of microphase separated diblock copolymers in shear flow. *Journal of Chemical Physics*, 128(12).

- Psachoulia, E., & Sansom, M. S. P. (2008). Interactions of the pleckstrin homology domain with phosphatidylinositol phosphate and membranes: Characterization via molecular dynamics simulations. *Biochemistry*, 47(14), 4211-4220.

- Sharma, V., Wikstrom, M., & Laakkonen, L. (2008). Modeling the active-site structure of the cbb(3)-type oxidase from Rhodobacter sphaeroides. *Biochemistry*, 47(14), 4221-4227.

- Winters, D. L., Autry, J. M., Svensson, B., & Thomas, D. D. (2008). Interdomain fluorescence resonance energy transfer in SERCA probed by cyan-fluorescent protein fused to the actuator domain. *Biochemistry*, 47(14), 4246-4256.

- Srairi-Abid, N., Kaabi, H., Mlayah-Bellalouna, S., Mejri, T., Sampieri, F., & El Ayeb, M. (2008). Immunological characterization of a non-toxic peptide conferring protection against the toxic fraction (AahG50) of the Androctonus australis hector venom. *Toxicon*, 51(3), 353-362.

- Schweinsberg, S., Moll, D., Burghardt, N. C. G., Hahnefeld, C., Schwede, F., Zimmermann, B., et al. (2008). Systematic interpretation of cyclic nucleotide binding studies using KinetXBase. *Proteomics*, 8(6), 1212-1220.

- Puiatti, M., Vera, D. M. A., & Pierini, A. B. (2008). Species with negative electron affinity and standard DFT methods. Finding the valence anions. *Physical Chemistry Chemical Physics*, 10(10), 1394-1399.

List of papers citing NAMD: A literature search in the ISI Web of Science citation database in April 2008 yielded 861 published journal articles, papers, or books citing the current [11] or prior [10] NAMD origin papers. Below are 25 recent cites:

- Kang, Y., Wang, Q., Liu, Y. C., Wu, T., Chen, Q., & Guan, W. J. (2008). Dynamic mechanism of collagen-like peptide encapsulated into carbon nanotubes. *Journal of Physical Chemistry B*, 112(15), 4801-4807.

- Southern, J., Pitt-Francis, J., Whiteley, J., Stokeley, D., Kobashi, H., Nobes, R., et al. (2008). Multi-scale computational modelling in biology and physiology. *Progress in Biophysics & Molecular Biology*, 96(1-3), 60-89.

- Zhao, Q., Comer, J., Dimitrov, V., Yemenicioglu, S., Aksimentiev, A., & Timp, G. (2008). Stretching and unzipping nucleic acid hairpins using a synthetic nanopore. *Nucleic Acids Research*, 36(5), 1532-1541.

- Langham, A. A., Ahmad, A. S., & Kaznessis, Y. N. (2008). On the nature of antimicrobial activity: A model for protegrin-1 pores. *Journal of the American Chemical Society*, 130(13), 4338-4346.

- Klauda, J. B., Roberts, M. F., Redfield, A. G., Brooks, B. R., & Pastor, R. W. (2008). Rotation of lipids in membranes: Molecular dynamics simulation, P-31 spin-lattice relaxation, and rigid-body dynamics. *Biophysical Journal*, 94(8), 3074-3083.

- Kozakiewicz, A., Neurnann, P., Banach, M., Komoszyiski, M., & Wojtczak, A. (2008). Modeling studies of potato nucleoside triphosphate diphosphohydrolase NTPDase1: an insight into the catalytic mechanism. *Acta Biochimica Polonica*, 55(1), 141-150.

- Cheng, M. H., Coalson, R. D., & Cascio, M. (2008). Molecular dynamics simulations of ethanol binding to the transmembrane domain of the glycine receptor: Implications for the channel potentiation mechanism. *Proteins-Structure Function and Bioinformatics*, 71(2), 972-981.

- Foley, M. C., & Schlick, T. (2008). Simulations of DNA Pol lambda R517 mutants indicate 517's crucial role in ternary complex stability and suggest DNA slippage origin. *Journal of the American Chemical Society*, 130(12), 3967-3977.

- Anselmi, C., Centini, M., Maggiore, M., Gaggelli, N., Andreassi, M., Buonocore, A., et al. (2008). Non-covalent inclusion of ferulic acid with alpha-cyclodextrin improves photo-stability and delivery: NMR and modeling studies. *Journal of Pharmaceutical and Biomedical Analysis*, 46(4), 645-652.

- Mukhopadhyay, B. P., Ghosh, B., Bairagya, H. R., Nandi, T. K., Chakrabarti, B., & Bera, A. K. (2008). Molecular modeling of the ternary complex of rusticyanin-cytochrome c(4)-cytochrome oxidase: An insight to possible H-bond mediated recog-

nition and electron transfer reaction in T. ferrooxidans. *Journal of Biomolecular Structure & Dynamics*, 25(5), 543-551.

- Hess, B., Kutzner, C., van der Spoel, D., & Lindahl, E. (2008). GROMACS 4: Algorithms for highly efficient, load-balanced, and scalable molecular simulation. *Journal of Chemical Theory and Computation*, 4(3), 435-447.

- Cherezov, V., Liu, W., Derrick, J. P., Luan, B., Aksimentiev, A., Katritch, V., et al. (2008). In meso crystal structure and docking simulations suggest an alternative proteoglycan binding site in the OpcA outer membrane adhesin. *Proteins-Structure Function and Bioinformatics*, 71(1), 24-34.

- Zhou, Y. G., Guan, L., Freites, J. A., & Kaback, H. R. (2008). Opening and closing of the periplasmic gate in lactose permease. *Proceedings of the National Academy of Sciences of the United States of America*, 105(10), 3774-3778.

- Venkatramani, R., & Radhakrishnan, R. (2008). Computational study of the force dependence of phosphoryl transfer during DNA synthesis by a high fidelity polymerase. *Physical Review Letters*, 1(8).

- Treptow, W., Marrink, S. J., & Tarek, M. (2008). Gating motions in voltage-gated potassium channels revealed by coarse-grained molecular dynamics simulations. *Journal of Physical Chemistry B*, 112(11), 3277-3282.

- Eriksson, M., Lindhorst, T. K., & Hartke, B. (2008). Differential effects of oligosaccharides on the hydration of simple cations. *Journal of Chemical Physics*, 128(10).

- Pereverzev, Y. V., Gunnerson, K. N., Prezhdo, O. V., Sullivan, P. A., Liao, Y., Olbricht, B. C., et al. (2008). Guest-host cooperativity in organic materials greatly enhances the nonlinear optical response. *Journal of Physical Chemistry C*, 112(11), 4355-4363.

- Li, Z. Y., Yu, H. B., Zhuang, W., & Mukamel, S. (2008). Geometry and excitation energy fluctuations of NMA in aqueous solution with CHARMM, AMBER, OPLS, and GROMOS force fields: Implications for protein ultraviolet spectra simulation. *Chemical Physics Letters*, 452(1-3), 78-83.

- Frangeul, A., Bussetta, C., Deval, J., Barral, K., Alvarez, K., & Canard, B. (2008). Gln151 of HIV-1 reverse transcriptase acts as a steric gate towards clinically relevant acyclic phosphonate nucleotide analogues. *Antiviral Therapy*, 13(1), 115-124.

- Singh, A., Kushwaha, H. R., & Sharma, P. (2008). Molecular modelling and comparative structural account of aspartyl beta-semialdehyde dehydrogenase of Mycobacterium tuberculosis (H37Rv). *Journal of Molecular Modeling*, 14(4), 249-263.

- Bhattacharya, S., Hall, S. E., Li, H., & Vaidehi, N. (2008). Ligand-stabilized conformational states of human beta(2) adrenergic receptor: Insight into G-protein-coupled receptor activation. *Biophysical Journal*, 94(6), 2027-2042.

- Perumal, S., Antipova, O., & Orgel, J. (2008). Collagen fibril architecture, domain organization, and triple-helical conformation govern its proteolysis. *Proceedings of the National Academy of Sciences of the United States of America*, 105(8), 2824-2829.

- Ma, B., & Levine, A. J. (2007). Probing potential binding modes of the p53 tetramer to DNA based on the symmetries encoded in p53 response elements. *Nucleic Acids Research*, 35(22), 7733-7747.

- Solares, S. D. (2008). Characterization of deep nanoscale surface trenches with AFM using thin carbon nanotube probes in amplitude-modulation and frequency-force-modulation modes. *Measurement Science & Technology*, 19(1).

- Rodriuez-Ropero, F., Zanuy, D., Casanovas, J., Nussinov, R., & Aleman, C. (2008). Application of 1-aminocyclohexane carboxylic acid to protein nanostructure computer design. *Journal of Chemical Information and Modeling*, 48(2), 333-343.

List of papers citing BioCoRE: A literature search in April 2008 of the Scopus citation database yielded the following citations of the BioCoRE origin paper [148]:

- Sild S, Maran U, Lomaka A, & Karelson M. (2006). Open computing grid for molecular science and engineering. *Journal of Chemical Information and Modeling*, 46(3): 953-959.

- Mecham, J., Clement, M., Snell, Q., Freestone, T., Seppi, K., & Crandall, K. (2006). Jumpstarting phylogenetic analysis. *International Journal of Bioinformatics Research and Applications*, 2(1), 19-35.

- Phillips, J. C., R. Braun, W. Wang, J. Gumbart, E. Tajkhorshid, E. Villa, C. Chipot, R. D. Skeel, L. Kale, & K. Schulten. (2005). Scalable molecular dynamics with NAMD. *Journal of Computational Chemistry*, 26(16): 1781-1802.

- Benedyczak, K., Wroński, M., Nowinski, A., Nowiński, K. S., Wypychowski, J., & Baa, P. (2005). UNICORE as uniform grid environment for life sciences. *Lecture Notes in Computer Science*, 3470:364-373.

- Zhongwu, Z., Feng, W., & Todd, B. D. (2005). Development of chemistry portal for grid-enabled molecular science. *Proceedings - First International Conference on e-Science and Grid Computing, e-Science 2005*, 2005:48-55.

- Chin Jr., G., E. G. Stephan & D. K. Gracio (2004). Computing through scientific abstractions in SysBioPSE. *Proceedings of the IEEE International Conference on Systems, Man and Cybernetics*, 1:70-75.

- Chin Jr., G. & C. S. Lansing (2004). The biological sciences collaboratory. *Proceedings of the International Conference on Mathematics and Engineering Techniques in Medicine and Biological Sciences, METMBS'04*, pp. 91-97.

- Chin Jr., G. & C. S. Lansing (2004). Capturing and supporting contexts for scientific data sharing via the biological sciences collaboratory. *Proceedings of the ACM Conference on Computer Supported Cooperative Work, CSCW*, pp. 409-418.

- Wypychowski, J., Pytliński, J., Skorwider, L., Nazaruk, M., Benedyczak, K., Wronski, M., et al. (2004). Life sciences grid in eurogrid and grip projects. *New Generation Computing*, 22(2), 147-156.

- Dittrich, M., S. Hayashi, & K. Schulten. (2004). ATP hydrolysis in the beta(TP) and beta(DP) catalytic sites of F-1-ATPase. *Biophysical Journal*, 87(5): 2954-2967.

- Fudos, I. & I. Kyriazis (2004). Thin client access to a visualization environment. *Computational Science - Iccs 2004, Proceedings*, 3039: 258-263.

- Dittrich, M., S. Hayashi, et al. (2003). On the mechanism of ATP hydrolysis in F-1-ATPase. *Biophysical Journal*, 85(4): 2253-2266.

- Wang, Y., Can, T., Wang, Y.-F., & Su, J. (2003). Personalized annotation and information sharing in protein science with information-slips. *Proceedings of the IASTED International Conference on Information and Knowledge Sharing*, pp. 299-304.

- Pytliński, J., Skorwider, L., Benedyczak, K., Wroński, M., Baa, P., & Huber, V. (2003). Uniform access to the distributed resources for the computational chemistry using UNICORE. *Lecture Notes in Computer Science*, 2658:307-315.

- Phillips, R., M. Dittrich, & K. Schulten. (2002). Quasicontinuum representations of atomic-scale mechanics: From proteins to dislocations. *Annual Review of Materials Research*, 32: 219-233.

- Finholt, T. A. (2002). Collaboratories. *Annual Review of Information Science and Technology*, 36: 73-107.

Software Application Website Popularity

The appeal and usability of the Resource web site continues to bring in growing numbers of unique visitors. (A visitor is defined as an individual machine accessing a web page on

our site; note that this is a much more conservative and accurate method of measuring web traffic than mere web hits.)

In the past year (April 2007 - March 2008) the web site home pages for the Resources VMD[†], NAMD[‡], and BioCoRE[§] softwares showed substantial visitor traffic, as depicted in Table 1.

	Total	Month Avg.
VMD	236,553	19,712
NAMD	125,478	10,456
BioCoRE	28,171	2,4347

Table 1: Application web site visits

Further Access

Below we report additional access activities by the Resource. The Resource trained visiting scientists, provided user support, and conducted workshops that provided training on Resource software and computational cluster development.

- *Visitor Program*
  The Resource visitor program invites members of the biomedical community to come to the Resource and get training on Resource software, as well as expert analysis of Resource members for scientific research problems of interest to the visitor. From April 2006 to March 2007, the Resource has hosted 15 visitors[¶]. Visitors fund their visits, while the Resource contributes computing resources, facilities, and local expertise.

- *User Support*
  The Resource strives to release code of high quality, and to distribute bug-free software to the user community. Assisting use in assuring the integrity and reliability of our software is a local prototyping phase, in which Resource members make use of early releases of code and provide feedback to developers before broader release occurs. In terms of providing support to the continually expanding external

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

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

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

[¶] `http://www.ks.uiuc.edu/Overview/People/visitor.cgi`

user community (over 135,000 users)[‖], support is a major undertaking, and taken very seriously by the Resource. Our support guidelines call for the programmers to respond to all support inquiries within 48 hours of receipt or the next business day. Nontrivial inquiries may take longer, though we strive to respond within three business days.

- *Workshops*
  The Resource presented two workshops since May 2007, including two on-site and one online 'hands-on' workshops, and two cluster-building workshops, as described below:

  – November 5-7, 2007, a "Hands-on Workshop on Computational Biophysics,"[†] was hosted by Helix Systems[‡], Center for Information Technology at the NIH main campus in Bethesda, Maryland. At the workshop participants learned how to simulate biological and synthetic membrane channels, stretch proteins, make publication quality images and movies, and study their favorite biomolecules.

  – November 6 - 16, 2007, a collaborative workshop "School on Biomolecular Simulations"[§] involved a Resource member and Resource training materials working in cooperation with the Centre for Computational Materials Science, Jawaharlal Nehru Centre for Advanced Scientific Research[¶], in Bangalore, India. This workshop introduced methods and tools for setting up molecular simulations of biomolecules.

Seminars 2007-2008

Between May 2007 and April 2008 the Resource organized and hosted 24 seminars. An established institution on the University of Illinois campus, Resource seminars benefit students and faculty from the University of Illinois campus as well as other departments and institutions. Using financial support from the Beckman Institute and our NIH Resource grant, leading scientists from around the country and around the world are brought to the Beckman Institute to present their work. Resource members also present seminars on occasion. The seminars and their respective abstracts are all posted on the Resource

[‖] Based on total number of downloads of VMD and NAMD, and registered BioCoRE users

[†] `http://www.ks.uiuc.edu/Training/Workshop/Bethesda/`

[‡] `http://helix.nih.gov/`

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

[¶] `http://www.jncasr.ac.in/ccms/index.html`

web site and are also announced on the main page of the Resource website for greater publicity. Below is a list of the Resource seminars from the past year:

- April 21, 2008, Professor Ross C. Walker, University of California, San Diego, La Jolla, CA, *Insights into the Activation Pathway of the Adenovirus Protease Enzyme using Nudged Elastic Band Simulations*
- April 14, 2008, Dr. Wonhwa Cho, University of Illinois at Chicago, Chicago, IL, *Spatio-temporal Regulation of Cellular Processes by Lipids and Lipid-binding Proteins*
- April 7, 2008, Dr. John Rubinstein, The Hospital for Sick Children, Toronto, Ontario, Canada, *Electron Cryo-microscopy of ATP Synthase*
- March 26, 2008, Dr. Benoit Roux, University of Chicago, Chicago, IL, *Advances in Molecular Dynamics Simulations of Membranes*
- March 24, 2008, Professor Eric Darve, Stanford University, Palo Alto, CA, *Adaptive Methods for Free Energy Computation and Coarse-graining Strategies*
- February 25, 2008, Dr. Dax Fu, Brookhaven National Laboratory, Upton, NY, *Structure and Mechanism of the Zinc Transporter YiiP*
- February 12, 2008, Dr. David E. Shaw, D. E. Shaw Research and Center for Computational Biology and Bioinformatics, Columbia University, New York, NY, *Toward Millisecond-Scale Molecular Dynamics Simulations of Proteins*
- December 17, 2007, Dr. Chirstophe Chipot, Nancy Universit, Cedex, France, Modeling *Induction Phenomena using an ab initio Polarizable Force Field*
- December 14, 2007, Dr. Franois Dehez, Nancy Universit, Cedex, France, *Ion Transport Through Synthetic Peptide Nanotubes*
- December 6, 2007, Professor Xiaowei Zhuang, Harvard University, Cambridge, MA, *Single Molecule and Super-Resolution of Biomolecules and Cells*
- December 5, 2007, Professor Xiaowei Zhuang, Harvard University, Cambridge, MA, *Zooming in on Single Molecules: Studying Protein-Nucleic Acid Interactions at the Single-Molecule Level*
- December 3, 2007, Professor Michael Wiener, University of Virginia, Charlottesville, VA, *TonB-Dependent Outer Membrane Transport: Structural Answers and Mechanistic Questions*

- November 29, 2007, Dr. Giacomo Fiorin, University of Pennsylvania, Philadelphia, PA, *Using Metadynamics to Understand the Mechanism of Calmodulin/target Recognition at Atomic Detail*
- November 29, 2007, Dr. Jerome Henin, University of Pennsylvania, Philadelphia, PA, *Membrane-based Action of Antimicrobial Oligomers: an Atomistic View*
- November 12, 2007, Professor Brian Kuhlman, University of North Carolina at Chapel Hill, Chapel Hill, NC, *Computer-based Design of Protein Structures and Interfaces*
- October 16, 2007, Dr. Sanghyun Park, Argonne National Laboratory, Argonne IL, *Statistical Mechanics of Tempering Simulations*
- October 8, 2007, Dr. Ron Dror, D. E. Shaw Research, New York, NY, *Scalable Algorithms for Fast Molecular Dynamics Simulation and Elucidation of Protein Function*
- September 17, 2007, Dr. Jizhong Lou, Georgia Institute of Technology, Atlanta, GA, *Structural Bases of Catch Bonds*
- September 10, 2007, Professor Toby Allen, University of California, Davis, Davis, CA, *Charged Protein Side Chains in Membranes: a Thermodynamic Perspective of Voltage Gated Ion Channel Activity*
- August 27, 2007, Professor Xi Chen, Columbia University, New York, NY, *Mechanisms of Gating of Mechanosensitive Channels of Large Conductance (MscL)*
- August 24, 2007, Dr. Aaron Oakley, Australian National University, Canberra, Australia, *A Molecular Mousetrap Determines Polarity of Termination of DNA Replication in E. coli*
- June 22, 2007, Dr. Bernard Lim, Mayo Clinic College of Medicine, Rochester, MN, *Atomic Force Microscopy of Blood Coagulation Proteins*
- June 22, 2007, Dr. Saraswathi Vishveshwara, Indian Institute of Science, Bangalore, India, *Dynamics of Protein Structure Networks*
- May 17, 2007, Professor Petros Koumoutsakos, ETH Zurich, Zurich Switzerland, *3 or 4 Easy Pieces*

Awards, Honors, and Special Recognitions

There are no items to list for the current year.

Dissemination

Broad-scale efforts in dissemination and outreach through the last year took advantage of a variety of available traditional and electronic delivery mechanisms, including: distribution of Resource-produced papers and know-how via the web site; talks, meetings, workshops, and conferences; software distribution; news stories and press releases; development of a YouTube movie gallery; and use of Resource images and movies in a variety of third-party publications and academic presentations. Specific accomplishments in dissemination over the last year include:

- 55 articles (published or in press) in refereed journals or other publications
- Over 870,000 unique visitors to the Resource web site
- 21,670 article downloads from the Resource's publications database
- 657 reprint requests fulfilled by Resource staff
- 45 talks by Resource faculty and 22 presentations by other members
- 43 news stories about the Resource in various media outlets
- 52 requests to use Resource images or movies from external publishers or presenters
- Over 7,300 views of the Resource's YouTube movie gallery

Following in sections below are details of the Resource's dissemination efforts.

Publications

Below is a list of 37 articles by Resource members and collaborators published over the last year, followed by a list of 18 articles currently in press.

Published Articles:

- A. Arkhipov, J. Hüve, M. Kahms, R. Peters, and K. Schulten. Continuous fluorescence microphotolysis and correlation spectroscopy using 4Pi microscopy. *Biophysical Journal*, 93:4006 - 4017, 2007.
- L. Celik, B. Schiøtt, and E. Tajkhorshid. Substrate binding and formation of an occluded state in the leucine transporter. *Biophysical Journal*, 94:1600 - 1612, 2008.
- V. Cherezov, W. Liu, J. Derrick, B. Luan, A. Aksimentiev, V. Katruc, and M. Caffrey. In meso crystal structure and computer simulations suggest an alternative proteoglycan binding site in the OpcA outer membrane adhesin. *PROTEINS: Structure, Function, and Bioinformatics*, 71:24 - 34, 2008.

- C. Chipot and K. Schulten. Understanding structure and function of membrane proteins using free energy calculations. In Eva Pebay-Peyroula, editor, *Biophysical analysis of membrane proteins. Investigating structure and function*, pp. 187–211. Wiley, Weinheim, 2008.

- J. Cohen and K. Schulten. O_2 migration pathways are not conserved across proteins of a similar fold. *Biophysical Journal*, 93:3591 - 3600, 2007.

- J. Cohen, K. W. Olsen, and K. Schulten. Finding gas migration pathways in proteins using implicit ligand sampling. In Robert K. Poole, editor, *Globins and other NO-reactive Proteins in Microbes, Plants and Invertebrates*, volume 437 of *Methods in Enzymology*, pp. 437–455. Elsevier, 2008.

- S. Cui, J. Yu, F. Kühner, K. Schulten, and H. E. Gaub. Double stranded DNA dissociates into single strands when dragged into a poor solvent. *Journal of the American Chemical Society*, 129:14710 - 14716, 2007.

- F. Dehez, J. G. Angyan, I. S. Gutierrez, F. J. Luque, K. Schulten, and C. Chipot. Modeling induction phenomena in intermolecular interactions with an ab initio force field. *Journal of Chemical Theory and Computation*, 3:1914 - 1926, 2007.

- J. Eargle, A. A. Black, A. Sethi, L. G. Trabuco, and Z. Luthey-Schulten. Dynamics of Recognition between tRNA and elongation factor Tu. *Journal of Molecular Biology*, 377:1382 - 1405, 2008.

- P. L. Freddolino, F. Liu, M. Gruebele, and K. Schulten. Ten-microsecond MD simulation of a fast-folding WW domain. *Biophysical Journal*, 94:L75 - L77, 2008.

- J. Gumbart and K. Schulten. Structural determinants of lateral gate opening in the protein translocon. *Biochemistry*, 46:11147 - 11157, 2007.

- J. Gumbart, M. C. Wiener, and E. Tajkhorshid. Mechanics of force propagation in TonB-dependent outer membrane transport. *Biophysical Journal*, 93:496 - 504, 2007.

- J. Henin, E. Tajkhorshid, K. Schulten, and C. Chipot. Diffusion of glycerol through Escherichia coli aquaglyceroporin GlpF. *Biophysical Journal*, 94:832 839, 2008.

- S. Hohng, R. Zhou, M. K. Nahas, J. Yu, K. Schulten, D. M. J. Lilley, and T. Ha. Mapping the two-dimensional reaction landscape of Holliday junction via dynamic fluorescence-force spectroscopy. *Science*, 318:279 283, 2007.

- T. A. Isgro and K. Schulten. Cse1p binding dynamics reveal a novel binding pattern for FG-repeat nucleoporins on transport receptors. *Structure*, 15:977 991, 2007.

- M. Ø. Jensen, Y. Yin, E. Tajkhorshid, and K. Schulten. Sugar transport across lactose permease probed by steered molecular dynamics. *Biophysical Journal*, 93:92 102, 2007.

- B. J. Johnson, J. Cohen, R. W. Welford, A. R. Pearson, K. Schulten, J. P. Klinman, and C. M. Wilmot. Exploring molecular oxygen pathways in Hanseluna Polymorpha copper-containing amine oxidase. *Journal of Biological Chemistry*, 282:17767 17776, 2007.

- I. Kosztin and K. Schulten. Molecular dynamics methods for bioelectronic systems in photosynthesis. In Thijs Aartsma and Joerg Matysik, editors, *Biophysical Techniques in Photosynthesis II*, volume 26 of *Advances in Photosynthesis and Respiration*, pp. 445-464. Springer, Dordrecht, 2008.

- E. H. Lee, J. Hsin, O. Mayans, and K. Schulten. Secondary and tertiary structure elasticity of titin Z1Z2 and a titin chain model. *Biophysical Journal*, 93:1719 1735, 2007.

- B. Lim, E. H. Lee, M. Sotomayor, and K. Schulten. Molecular basis of fibrin clot elasticity. *Structure*, 16:449459, 2008.

- B. Luan, M. Caffrey, and A. Aksimentiev. Structure refinement of the OpcA adhesin using molecular dynamics. *Biophysical Journal*, 93:3058-3069, 2007.

- Y. Z. Ohkubo and E. Tajkhorshid. Distinct structural and adhesive roles of Ca2+ in membrane binding of blood coagulation factors. *Structure*, 16:72-81, 2007.

- John D. Owens, Mike Houston, David Luebke, Simon Green, John E. Stone, and James C. Phillips. GPU computing. *Proceedings of the IEEE*, 96:879899, 2008.

- K. Schulten, J. C. Phillips, L. V. Kalé, and A. Bhatele. Biomolecular modeling in the era of petascale computing. In David Bader, editor, *Petascale Computing: Algorithms and Applications*, pp. 165181. Chapman and Hall/CRC Press, Taylor and Francis Group, New York, 2008.

- M. K. Sener, J. D. Olsen, C. N. Hunter, and K. Schulten. Atomic level structural and functional model of a bacterial photosynthetic membrane vesicle. *Proceedings of the National Academy of Sciences,* USA, 104:1572315728, 2007. bf PMCID: 2000399.

- A. Y. Shih, A. Arkhipov, P. L. Freddolino, S. G. Sligar, and K. Schulten. Assembly of lipids and proteins into lipoprotein particles. *Journal of Physical Chemistry B*, 111:1109511104, 2007.

- A. Y. Shih, P. L. Freddolino, S. G. Sligar, and K. Schulten. Disassembly of nanodiscs with cholate. *Nano Letters*, 7:16921696, 2007.
- G. Sigalov, J. Comer, G. Timp, and A. Aksimentiev. Detection of DNA sequences using an alternating electric field in a nanopore capacitor. *Nano Letters*, 8:56-63, 2008.
- M. Sotomayor and K. Schulten. Single-molecule experiments in vitro and in silico. *Science*, 316:11441148, 2007.
- J. E. Stone, J. C. Phillips, P. L. Freddolino, D. J. Hardy, L. G. Trabuco, and K. Schulten. Accelerating molecular modeling applications with graphics processors. *Journal of Computational Chemistry*, 28:26182640, 2007.
- L. G. Trabuco, E. Villa, K. Mitra, J. Frank, and K. Schulten. Flexible fitting of atomic structures into electron microscopy maps using molecular dynamics. *Structure*, 16:673–683, 2008.
- V. Vasquez, M. Sotomayor, D. M. Cortes, B. Roux, K. Schulten, and E. Perozo. Three dimensional architecture of membrane-embedded MscS in the closed conformation. *Journal of Molecular Biology*, 378:5570, 2008.
- Y. Wang and E. Tajkhorshid. Molecular mechanisms of conduction and selectivity in aquaporin water channels. *Journal of Nutrition*, 137:1509S-1515S, 2007.
- D. Wells, V. Abramkina, and A. Aksimentiev. Exploring transmembrane transport through alpha-hemolysin with grid-steered molecular dynamics. *Journal of Chemical Physics*, 127:125101-125110, 2007.
- J. Yu, T. Ha, and K. Schulten. How directional translocation is regulated in a DNA helicase motor. *Biophysical Journal*, 93:37833797, 2007.
- Q. Zhao, J. Comer, S. Yemenicioglu, A. Aksimentiev, and G. Timp. Stretching and unzipping nucleic acid hairpins using a synthetic nanopore. *Nucleic Acids Research*, 36:1532-1541, 2008. PMCID: 2275135.
- Q. Zhao, G. Sigalov, V. Dimitrov, B. Dorvel, U. Mirsaidov, S. Sligar, A. Aksimentiev, and G. Timp. Detecting SNPs using a synthetic nanopore. *Nano Letters*, 7:1680-1685, 2007.

Articles In Press

- A. Aksimentiev, R. Brunner, J. Cohen, J. Comer, E. Cruz-Chu, D. Hardy, A. Rajan, A. Y. Shih, G. Sigalov, Y. Yin, and K. Schulten. Computer modeling in

biotechnology, a partner in development. In *Protocols in Nanostructure Design, Methods in Molecular Biology*. Humana Press, 2008. In press.

- A. Bhatele, S. Kumar, C. Mei, J. C. Phillips, G. Zheng, L. V. Kalé, Overcoming Scaling Challenges in Biomolecular Simulations across Multiple Platforms, *Proceedings of IEEE International Parallel and Distributed Processing Symposium 2008*, Miami, Florida, USA, April 2008. In press.

- Z. Chen, J. Lou, C. Zhu, and K. Schulten. Flow induced structural transition in the β-switch region of glycoprotein Ib. *Biophysical Journal*, 2008. In press.

- J. Diao and E. Tajkhorshid. Indirect role of Ca2+ in the assembly of extracellular matrix proteins. *Biophysical Journal*, 2008. In press.

- P. L. Freddolino, A. Arkhipov, A. Y. Shih, Y. Yin, Z. Chen, and K. Schulten. Application of residue-based and shape-based coarse graining to biomolecular simulations. In Gregory A. Voth, editor, *Coarse-Graining of Condensed Phase and Biomolecular Systems*. Chapman and Hall/CRC Press, Taylor and Francis Group, 2008. In press.

- B. Isin, K. Schulten, E. Tajkhorshid, and I. Bahar. Mechanism of signal propagation upon retinal isomerization: Insights from molecular dynamics simulations of rhodopsin restrained by normal modes. *Biophysical Journal*, 2008. In press.

- S. Kumar, C. Huang, G. Zheng, E. Bohm, A. Bhatele, J. C. Phillips, H. Yu, and L. V. Kalé. Scalable molecular dynamics with NAMD on the IBM Blue Gene/L system. *IBM Journal of Research and Development*, 2008. In press.

- C. W. Lee and C. Mendes, L. V. Kalé, Towards Scalable Performance Analysis and Visualization through Data Reduction, *13th International Workshop on High-Level Parallel Programming Models and Supportive Environments*, Miami, Florida, USA, April 2008. In press.

- J. H. Morrissey, V. Pureza, R. L. Davis-Harrison, S. G. Sligar, Y. Z. Ohkubo, and E. Tajkhorshid. Blood clotting reactions on nanoscale phospholipid bilayers. *Thrombosis Research*, 2008. In press.

- A. Rajan, M. S. Strano, D. A. Heller, T. Hertel, and K. Schulten. Length dependent optical effects in single walled carbon nanotubes. *Journal of Physical Chemistry B*, 2008. In press.

- C. I. Rodrigues, D. J. Hardy, J. E. Stone, K. Schulten, and W-M. W. Hwu. GPU acceleration of cutoff pair potentials for molecular modeling applications. *Proceedings of the 2008 Conference On Computing Frontiers*, 2008. In press.

- M. K. Sener and K. Schulten. From atomic-level structure to supramolecular organization in the photosynthetic unit of purple bacteria. In C. Neil Hunter, Fevzi Daldal, Marion C. Thurnauer, and J. Thomas Beatty, editors, *The Purple Phototrophic Bacteria*, chapter 16. Springer, 2008. In press.

- A. Y. Shih, P. L. Freddolino, A. Arkhipov, S. G. Sligar, and K. Schulten. Molecular modeling of the structural properties and formation of high-density lipoprotein particles. In Scott Feller, editor, *Current Topics in Membranes: Computational Modeling of Membrane Bilayers*. Elsevier, 2008. In press.

- A. Y. Shih, S. G. Sligar, and K. Schulten. Molecular models need to be tested: the case of a solar flares discoidal HDL model. *Biophysical Journal*, 2008. In press.

- I. A. Solov´ yov, D. Chandler, and K. Schulten. Exploring the possibilities for radical pair effects in cryptochrome. *Plant Signaling and Behavior*, 2008. In press.

- M. Sotomayor and K. Schulten. The allosteric role of the Ca++ switch in adhesion and elasticity of C-cadherin. *Biophysical Journal*, 2008. In press.

- T. Vosegaard, K. Bertelsen, J. M. Pedersen, L. Thøgersen, B. Schiøtt, E. Tajkhorshid, T. Skrydstrup, and N. Chr. Nielsen. Resolution enhancement in solid-state NMR spectra of oriented membrane proteins by anisotropic differential linebroadening. *Journal of the American Chemical Society*, 2008. In press.

- Y. Wang, Y. Z. Ohkubo, and E. Tajkhorshid. Gas conduction of lipid bilayers and membrane channels. In Scott Feller, editor, *Current Topics in Membranes: Computational Modeling of Membrane Bilayers*. Elsevier, 2008. In press.

Web Site Design and Popularity

The amount of traffic to the Resource website, as well as links to the web site from other groups, are telling indicators of the success of Resource outreach efforts. Details on visits and links to the site are provided below.

There have been 870,204 unique visitors to the Resource web site, an average of 89,360 per month during the April 2007 - March 2008 period; visits in March 2008 alone resulted in 199 gigabytes of data transfer (from downloaded pages, images, and files within the site, and excluding robots, worms, or replies with special HTTP status codes). The most visited sections of the web site are shown in Table 2.

A recent Yahoo! site search (April, 2008) found that 15,084 external sites link into areas of the Resource web site, with 1,035 site linking directly to the home page.

	Total Visitors	Visitors per Month
VMD	236,553	26,118
NAMD	125,478	14,610
BioCoRE	28,171	3,281
Other Research	153,274	15,584
Galleries	42,756	4,363
Publications	38,717	3,226
Seminars	6,228	519

Table 2: Web site visitors from April 2007 - March 2008

An example service found at the Resource web site is the publications database*, which provides visitors with a searchable database of Resource publications, including searches by title, author(s), journal, subject, year ranges, and fulltext searching. Over 21,670 unique visitors downloaded at least one file copy of an article using the database over the April 2007 - March 2008 period. Additionally, 657 reprint requests were handled directly by Resource staff, primarily by posting electronic files in a manner that respects copyright restrictions.

Lectures, Presentations and Posters

The Resource PIs and other members gave the following lectures, presentations, or posters over the last year†:

Klaus Schulten

- May 2008, University of Illinois, Urbana, 2008 NCSA Private Sector Program Annual Meeting, "The Computational Microscope"
- May 2008, Physics Department, University of Illinois at Urbana-Champaign, UCS, 2008, "Brownian Ratchet Seen in Action: How Directional Translocation is Regulated by a DNA Helicase Motor"
- April 2008, Indianapolis, IN, Eli Lily, Global Drug Discovery Group, "Advances in Molecular Dynamics Simulations"
- April 2008, St. Louis, MO, Washington University in St. Louis, Department of Biochemistry and Molecular Biophysics, "How Directional Translocation is Regulated by a DNA Helicase Motor"

*http://www.ks.uiuc.edu/Publications/Papers/

†http://www.ks.uiuc.edu/Publications/Lectures/lectures.cgi

- February 2008, Salt Lake City, UT, University of Utah, Physical Chemistry Colloquium, "The Computational Microscope"
- February 2008, Long Beach, CA, 2008, 52nd Biophysical Society Annual Meeting & 16th IUPAB Intl Congress, "Observing Protein Translocation in SecY and a SecY-Ribosome Complex through Molecular Dynamics"
- January 2008, Steamboat Springs, CO, Keystone Symposia J1 2008 - Frontiers of Structural Biology, "The Computational Microscope"
- December 2007, Berkeley, CA, UC Berkeley, Department of Chemistry, Berkeley Structural and Quantitative Biology seminar series, "Multiscale Modeling of Cellular Systems"
- November 2007, San Diego, CA, The Scripps Research Institute, Workshop on Advanced Topics in EM Structure Determination, "Fitting Crystallographic Structures into EM Density Maps. Analyzing Results through Physical Modeling and Computer Graphics"
- November 2007, University of California, Irvine, Institute for Genomics and Bioinformatics, Distinguished Speaker Series, "The Computational Microscope"
- November 2007, Bethesda, MD, National Institutes of Health, Computational Biophysics Workshop, "Statisical Mechanics of Proteins" and "Molecular Dynamics of Cellular Processes II"
- October 2007, University of California, San Diego, CA, Physical Chemistry Seminar, "Life under Tension: The Mechanical Forces of Proteins"
- October 2007, Stanford University, Palo Alto, CA, Student Hosted Physical Chemistry Colloquia Series, "Life Under Tension"
- October 2007, Stanford University, Palo Alto, CA, Life in Motion, Bio-X Symposium 2007,"Computational Approach to Structural Systems Biology"
- September 2007, Upton, NY, Brookhaven National Lab, Computational Biology/Bioenergy Workshop and Mini-Symposium, "Multiscale Biomolecular Modeling from Molecules to Cells"
- September 2007, South Kensington, London, UK, Imperial College, Workshop on Multiscale Modelling in Biomolecular Systems, "Amino Acid-based and Shape-based Forward and Backward Coarse Graining Strategies for ms Simulation of Lipid-protein and Protein-protein Assemblies"

- August 2007, Boston, MA, 234th ACS National Meeting & Exposition, "From Megaflops to Teraflops: From Molecules to Cells"
- August 2007, Boston, MA, 234th ACS National Meeting & Exposition, "Computational Microscopy Merging Crystallographic and Electron Microscope Images"
- August 2007, Breckenridge, CO, The 8th International Hydrogenase Conference, "A Simulation-based Approach for Designing an O2-tolerant Hydrogenase"
- August 2007, Urbana, Illinois, University of Illinois, CCM Summer Course Cell Mechano-sensitivity, "Life Under Tension"
- July 2007, Urbana, IL, University of Illinois, NCSA, Multicore Workshop, "Early user Experience on the Abe Parallel Computer with NAMD"
- July 2007, Boston, MA, 21st Symposium of the Protein Society, "Studying Protein Elasticity and Unfolding by Single Molecule Experiments in vitro and in silico"
- July 2007, Munich, Germany, Technical University of Munich, "The Computational Microscope"
- June 2007, Keystone, Co, Summit on Biomechanics, "Molecular Mechanisms Underlying the Mechanics of Living Cells"
- June 2007, Albany, NY, Howard Hughes Medical Institute, Mini-Symposium on Molecular Machines and the Biology of Movement, "Picosecond-to-millisecond Computational Modeling of the Small Motor Protein PcrA Helicase"
- May 2007, Santa Fe, New Mexico, 27th Annual Conference of the Center for Nonlinear Studies, Complexity of Biological and Soft Materials, "How Directional Translocation is Regulated by a DNA Helicase Motor"
- May 2007, Urbana, IL, University of Illinois, Department of Physics, Understanding Complex Systems, "Pruning Degrees of Freedom in Biomolecular Dynamics Simulations through Coarse-graining and Continuum Approaches"
- May 2007, Bethesda, Maryland, National Institutes of Health, Structural Biology Interest Group Seminar, "The Computational Microscope"
- May 2007, Austin, Texas, University of Texas, Distinguished Lecture Series in Petascale Simulation, "Petascale Computing in the Biosciences - Simulating Entire Life Forms"
- May 2007, Los Angeles, CA, University of California Los Angeles, Department of Physics and Astronomy Colloquium, "The Computational Microscope"

- April 2007, Davis, California, University of California, Davis, Department of Applied Science, "Petascale Computing in the Biosciences - Simulating Entire Life Forms"

Emad Tajkhorshid

- March 2008, Ventura, CA, Gordon Research Conference - Ligand Recognition and Molecular Gating, "Dynamics of Substrate Binding, Gating, and Energy Coupling in Membrane Transporters"
- January 2008, Urbana, IL, University of Illinois at Urbana-Champaign, Departmental Seminar, "Membrane Transport at sub-Angstrom Resolution"
- November 2007, Bethesda, MD, National Institutes of Health, Computational Biophysics Workshop, "Introduction to Protein Structure and Dynamics" and "Molecular Dynamics of Cellular Processes I"
- November 2007, West Lafayette, IN, Purdue University, "Membrane Transport at sub-Angstrom Resolution"
- August 2007, Boston, MA, 234th ACS National Meeting, "Large-scale Simulations of Gating and Transport in Membrane Channels and Transporters"
- July 2007, Urbana, IL, University of Illinois, National Center for Supercomputing Applications, Experimental and Computational Approaches to Understanding Membrane Assemblies and Permeation, "Multiscale Methods to Simulate Membrane Organization: Combining All-atom and Coarse-grained Models to Simulate Transport Across Lipid Bilayers"
- June 2007, Park City, UT, Membranes and Membrane Proteins Meeting, "Treble Role of Calcium in Membrane Binding of Blood Coagulation Factors"

Alek Aksimentiev

- April 2008, Columbia, MO, University of Missouri at Columbia, Department of Physics and Astronomy, O. M. Stewart Colloquia, "Solid-state Nanopores: Versatile Instruments for Nanotechnology and Life Sciences"
- November 2007 Syracuse, NY, Syracuse University, Department of Physics, Condensed Matter and Biological Physics Seminar, "Synthetic Nanopores for Sequencing DNA"

- September 2007, Lyon, France, CECAM workshop on Ionic Transport: from Nanopores to Biological Channels, "Electric Field-driven Transport of DNA Through Biological and Synthetic Nanopores"
- September 2007, Ile de Berder, France, Summer school: Biosensing with Channels, "In Silico Single Molecule Recordings Using Biological and Artificial Nanopores"
- August 2007, Boston, MA, American Chemical Society Meeting, "All-atom and Multiscale Modeling of Silicon Bionanodevices"

Other TCB members (includes meetings attended and poster sessions)

- March, 2008, Macomb, IL, Western Illinois University Physics Department, "Bringing Physics to Life: Biological Insights from Computer Simulations" (James Gumbart)
- March 2008, New Orleans, LA, American Physical Society March Meeting, "Diffusion Limited Optical Effects in Single Walled Carbon Nanotubes" (Aruna Rajan)
- March 2008, Atlanta, GA, SIAM Conference on Parallel Processing for Scientific Computing, "Accelerating Molecular Modeling Applications with Graphics Processors" (John Stone)
- March 2008, Telluride, CO. Tsrc Workshop on Mechanistic Analysis of Biological Systems with Novel Computational Models, "Maturation of high-density lipoprotein particles" (Amy Y. Shih)
- February 2008, Long Beach, CA, Biophysical Society 52nd Annual Meeting
  - Poster: "Ion Binding Sites of Acid Sensing Ion Channel-1" (Saher Afshan Shaikh, Emad Tajkhorshid)
  - Poster: "Multiscale Simulations of Membrane Tubulation by BAR Domains" (Ying Yin, Anton Arkhipov, Klaus Schulten)
  - Poster: "Where is the bc1-complex Located in the Photosynthetic Chromatophore?" (Chris Harrison, Danielle Chandler, Jen Hsin, James Gumbart, Klaus Schulten)
  - Poster: "The Allosteric Role of the Ca+2 switch in Adhesion and Elasticity of C-Cadherin" (Marcos Sotomayor, Klaus Schulten)
  - Poster: "Rhodobacter sphaeroides LH1-RC-PufX Dimer Curves Chromatophore Membranes" (Jen Hsin, James C. Gumbart, Danielle E. Chandler, Christopher Harrison, Pu Qian, Per A. Bullough, C. Neil Hunter, Klaus Schulten)

  - Poster: "FG repeatStructure of the Brush-like Mesh Formed by the FG-repeat Nucleoporin Nsp1" (Lingling Miao, Timothy A. Isgro, Klaus Schulten)
  - Poster: "Simulation of Protein Translocation Inside the Central Channel of Bacterial Flagellum" (Zhongzhou Chen, Peter Freddolino, Anton Arkhipov, Klaus Schulten)
  - Poster: "Complex Formation-Activation of Coagulation Factors at the Negatively Charged Membrane Surface" (Y. Zenmei Ohkubo, Zhijian Huang, Emad Tajkhorshid)
  - Poster: "Dissecting Lipid- and Protein-Mediated Exchange of Gas Molecules across Biological Membranes" (Yi Wang, Y. Zenmei Ohkubo, Emad Tajkhorshid)
  - Poster: "Extracellular Gating Mechanism of the Glutamate Transporter" (Zhijian Huang, Emad Tajkhorshid)
  - Poster: "The Maturation of Human High-Density Lipoprotein Particles: Conversion of Disks to Spheres" (Amy Y. Shih, Stephen G. Sligar, Klaus Schulten)
  - Poster: "The roles of the Pore Ring and the Plug in the SecY Protein-conducting Channel" (James Gumbart, Klaus Schulten)
  - Lecture (platform presentation): "Molecular Mechanism of Fibrin Clot Elasticity" (Eric Lee)
  - Lecture: "Gating Charge Calculations of the Kv1.2 Potassium Channel" (Fatemeh Khalili-Araghi)

- November 2007, Princeton, NJ, Princeton University, Institute for Advanced Study, AstroGPU 2007 Conference, "GPU Acceleration of Scientific Applications Using CUDA" (John Stone)
- November 2007, Reno, NV, SC07 International Conference on High Performance Computing, Networking, Storage, and Analysis, "High Performance Computing on GPUs with CUDA" (John Stone)
- October 2007, Urbana, IL, University of Illinois, ECE 498L1: Programming Massively Parallel Processors, "Case Studies: Ion Placement Tool, VMD" (John Stone)
- September 2007, Urbana, IL, Beckman Institute, Beckman Student Seminar Series, "Macromolecular Yoga: Merging Data from Different Resolutions to Reveal Biomolecular Function" (Elizabeth Villa)

Media Coverage

Stories involving the Resource appeared in popular media, scientific journals, online news sources, and more over the last year. Media coverage includes stories on Resource plans to use its NAMD software on the Texas Advanced Computing Center's Ranger machine to model 100 million atom chromatophores of purple bacteria[‡], the use of VMD and NVIDIA GPUs to conduct simulations of nano-devices that can be used to sequence DNA in real-time[§], and Resource development of a DNA sequencing technique that could cost as little as $1,000 per person[¶].

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Outreach

Resource efforts to reach the biomedical community in addition to the aforementioned media coverage, scholarly articles, lectures, posters, and workshops are viewed as "outreach" activities, and include items such as the following:

- On-site demonstrations
- Making images and movies available for use by others
- Responding to licensing requests

Demonstrations

Visitors to the Resource (e.g., seminar speakers, visiting scientists, others) are customarily provided with presentations of Resource science of interest to them using the Resource's visualization facility. Presentations typically involve three or more demonstrations provided by Resource staff members, postdocs, or graduate students. Each demonstration involves loading VMD-based images and/or movies into the Resource's 3D stereo projection system, and then discussing the science and computation behind what is shown. There were approximately 40 such presentations providing around 57 demonstrations during the May 2007 – April 2008 time period.

Image and Movie Gallery Requests

The Resource maintains at its web site galleries of images** and movies†† representing Resource research and developed using its VMD and NAMD software. On a frequent basis the Resource responds to requests from external scientists and others for permission to use the images and movies in a variety of media, including web sites, books, papers, press articles, talks and presentations. While typically a single image or movie is requested, on occasion one person will request multiple images or movies. From May 2007 – April 2008, 52 images or movies were requested for use by the external public. A standard response text, written in cooperation with university intellectual property representatives, grants non-exclusive permission to image and movie requests, which protects Resource copyright while at the same time allowing for image/movie distribution.

YouTube Movie Gallery

A new dissemination feature is the Resource's gallery of movies† at the popular YouTube‡ video hosting site. Begun in October 2007, the site currently contains a library of 10 videos. Akin to the design of the Resource's web site movie gallery, each movie after a title slide starts with a basic description of the phenomena to be viewed. At the end of the movie, viewers are directed to Resource web pages with more detailed information, links to the VMD web site, and an email address for inquiries. Further a license statement

**http://www.ks.uiuc.edu/Gallery/Science/Structure/

††http://www.ks.uiuc.edu/Gallery/Movies/

†http://www.youtube.com/tcbguiuc

‡http://www.youtube.com

(using the Creative Commons[§] framework) requires that the Resource be acknowledged when the movie is used, and that commercial use and derivative works are prohibited.

As of the end of April 2008, the most viewed movies were "Water Channels in Cell Membranes"[¶] with 1,909 views, and "Lipoproteins that Circulate in the Blood Collecting Fat"[‖] with 1,835 views. The total count of all views of all listed videos reached 7,339 views.

Licensing and Distribution

Resource software licenses, which already allow for broad use, are upon request reviewed and if needed revised to meet the needs of external groups. Such expansions are done in consultation and cooperation with the University of Illinois Office of Technology Management, who provide needed technical and legal expertise. Currently, the Resource is working with the University of Illinois Office of Vice Chancellor for Research to develop a staff position where responsibilities would include developing licenses for and marketing Resource software to the private sector.

[§] `http://creativecommons.org`

[¶] `http://www.youtube.com/watch?v=XxadMJ9zqpA`

[‖] `http://www.youtube.com/watch?v=Dbw0zhof0Ek`

Patents, Licenses, Inventions, and Copyrights

No patents, licenses, inventions or copyrights have been granted to Resource Primary Investigators or other members over the current reporting period.

Training

The Resource has continued and expanded its training efforts through workshops, tutorial updates, expanding its library of case studies, and hosting visitors. Whenever possible, training materials are made available via the Resource website for public consumption, and are tailored to support self-study. Such efforts are in addition to more traditional training programs for graduate students and postdoctoral researchers, as well as university classes. Training outcomes over the past 12 months include:

- Two workshops reaching over 80 participants
- Nearly 22,000 views of online tutorials
- Updates to Resource tutorials
- Nearly 6,500 views of online case studies
- Release of the "Light Harvesting Complex 2" case study
- 15 participants in the Resource's Visitor Program
- Doctoral and postdoctoral training
- Graduate and undergraduate classes taught by Resource faculty

Hands-On Workshops in Computational Biophysics

The Resource in the last year (May 2007 - April 2008) provided training via two hands-on workshops in computational biophysics. The 'hands-on' aspect of the workshop configuration refers to the curriculum of morning lectures being followed by afternoon tutorials where participants also get to work directly with their favorite biomolecules using the Resource's VMD and NAMD softwares. The workshops are designed for graduate students and postdoctoral researchers in computational and/or biophysical fields seeking to extend their research skills to include computational and theoretical expertise, as well as other researchers interested in theoretical and computational biophysics. Recent workshops include:

Bethesda Workshop[*].

Sponsored by Helix Systems[†] and held at the Center for Information Technology at NIH's Bethesda campus from November 5 - 7, 2007, the computational biophysics workshop

[*] `http://www.ks.uiuc.edu/Training/Workshop/Bethesda/`

[†] `http://helix.nih.gov/`

trained 30 participants both the craft and art of modeling through learning by doing. Participants learned how to stretch proteins, pull water through molecular channels, mine genomic data, and study their favorite biomolecules. Evaluation results indicate that 93% of participants found the workshop broadened their understanding of concepts and principles in the field of computational and theoretical biophysics, their ability to carry out research in that area, and that the techniques learned were directly applicable to their career. Evaluation-wise this was one of the most successful Resource workshops.

Bangalore Workshop[‡].

Sponsored by the Centre for Computational Materials Science[§] at the Jawaharlal Nehru Centre for Advanced Scientific Research in Bangalore, India, and held from November 6 - 16, 2007, the "School on Biomolecular Simulations" represented a collaborative workshop effort by the Resource. Instead of organizing all aspects and providing all content as in the Resource's standard workshop format, in this workshop a Resource member traveled to India to provide lectures and tutorials to 53 selected participants in coordination with lecturers from other institutions. The workshop largely used Resource tutorials and software, and also followed the 'hands-on' design as stated in the description of the workshop: "The morning sessions will have lectures introducing concepts and methods and the afternoon sessions will have computational exercises. The school will be based on freely available software NAMD (www.ks.uiuc.edu) and VMD"[¶].

Tutorials

Five tutorials were updated in content over the past year, to reflect changes in the VMD and NAMD software used by the tutorials, in response to comments from users of the tutorials, to provide additional materials, or for other reasons. Updated tutorials include:

- VMD Molecular Graphics Tutorial
- NAMD Molecular Dynamics/Steered Molecular Dynamics Tutorial
- Topology File Tutorial
- Simulation of Water Permeation Through Nanotubes Tutorial
- Stretching Deca-Alanine Tutorial

[‡] `http://www.ks.uiuc.edu/Training/Workshop/Bangalore/`

[§] `http://www.jncasr.ac.in/ccms/`

[¶] `http://www.jncasr.ac.in/ccms/sbs2007/`

For example, the Resource has been actively improving the VMD Molecular Graphics Tutorial, which is aimed at providing an introductory overview of how to use various features of VMD. Recently, a new version of the tutorial has been developed and submitted (upon invitation) to the book series *Current Protocols - Bioinformatics*, and is to be published shortly. This version incorporates several previous VMD tutorials, as well as new material, and focuses on the most popular VMD features including high-quality molecular image rendering, molecular dynamics movie making, analysis of protein sequence and structure, and molecular dynamics simulation analysis.

All tutorials, consisting of text (in PDF or html format) and associated files, produced by the Resource are made available online for public download and use[‖] at the Resource web site. For the PDF versions of the tutorials alone, web site statistics indicate that the top five most viewed tutorials over May 2007 - April 2008 are the NAMD Tutorial (6,064 views), VMD Molecular Graphics (5,664), VMD Images and Movies Tutorial (2,762), Topology File Tutorial (1,088 views), and Sequence Alignment Algorithms (1,090 views). Counts for all PDF versions of all tutorials indicate over 21,800 views during that same time period.

Case Studies

Added to the Resource's library of case studies[†] this year has been the *Light Harvesting Complex 2*[‡] case study:

"Sunlight is ultimately the energy source for nearly all life on Earth. Many organisms, such as plants, algae, and some bacteria, have developed a means to harvest sunlight and turn it into chemical energy, a process known as photosynthesis. Photosynthesis occurs with an amazingly high efficiency, not surprising given the more than 3.5 billion years of evolution..."

Case studies consist of text (in PDF format) and associated files, are produced by the Resource, and are made available online for public download and use[§] at the Resource web site. Web site statistics indicate that the top five most viewed case studies from May 2007 - April 2008 are the Water (1,114 views), Lipid Bilayer (1,027), DNA (897), Myoglobin (876 views), and Ion Channels (567 views) case studies. For all case studies combined, there were nearly 6,500 views.

Visitor Program

[‖] `http://www.ks.uiuc.edu/Training/Tutorials/`

[†] `http://www.ks.uiuc.edu/Training/CaseStudies/`

[‡] `http://www.ks.uiuc.edu/Training/CaseStudies/index.html#lh2cs`

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

The Resource visitor program provides scientists (who come with their own financial support) with the opportunity to learn how to use Resource-produced software, other software hosted on Resource computers, and to benefit from the knowledge and expertise of Resource members. Resource members spend substantial amounts of time helping visitors achieve their educational and research goals. At the end of their time at the Resource, visitors acquired critical skills and new experiences that they took back to their home laboratories. Visits may last for several days to several months; visitors to the Resource during the May 2007 - April 2008 period (listed by the month they started their visit) include:

- Basak Isin, University of Pittsburgh (April 2008)
- Melih Sener, Cornel University - Weill Medical College (January 2008)
- Xueqing Zou, Peking University (October 2007)
- Gloria Cardenas-Jiron, University of Santiago de Chile (January 2008)
- Wei Chen, Georgia Institute of Technology (September 2007)
- Christopher Chipot, Universite Henri Poincare (December 2007)
- Francois Dehez, Universite Henri Poincare (December 2007)
- Christine English, National Renewable Energy Laboratory (September 2007)
- Hai Long, National Renewable Energy Laboratory (September 2007)
- Jizhong Lou, Georgia Institute of Technology (September 2007)
- Paul McCreary, Evergreen State College (August 2007)
- Aaron Oakley, Australian National University (August 2007)
- Thorsten Ritz, University of California at Irvine (June 2007)
- Jan Saam, Institute of Biochemistry, Charite - Universittsmedizin Berlin, Germany (April 2007)
- Tomek Wlodarski, Jagiellonian University (July 2007)

Graduates

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

Ph.D. Recipients: Recent UIUC Ph.D. recipients who received their training at the Resource are listed below.

- Timothy Isgro, Ph.D., Physics, University of Illinois, Spring 2007
- Marcos Sotomayor, Ph.D., Physics, University of Illinois, Fall 2007
- Jin Yu, Ph.D., Physics, University of Illinois, Fall 2007
- Amy Shih, Ph.D., Biophysics, University of Illinois, Spring 2008
- Elizabeth Villa, Ph.D., Biophysics, University of Illinois, Spring 2008

Postdoctoral Associates: Postdoctoral associates that have recently received or are currently receiving training at the Resource are:

- David Hardy
- Chris Harrison
- Eduard Schreiner
- Jan Saam
- Amy Shih
- Elizabeth Villa

Classes Taught by Resource Faculty

Resource faculty also train the next generation of scientists through graduate and undergraduate level courses at the University of Illinois. Sample topics for courses taught in Fall 2007 - Spring 2008 are listed below.

- Biomolecular Physics
- Computational Chemical Biology
- Nonequilibrium Statistical Mechanics
- Computational Chemical Biology
- Medical Pharmacology
- University Physics and Mechanics

Resource Library

The Resource library, an important internal training resource, has been expanded by the purchase of 30 new books, bringing the total volume count to 1,000 books. Further, to supplement the UIUC librarys collection of on-line and print journals, the Resource subscribes to the following journals in science and computing:

- Physics Today
- Science
- Dr. Dobbs Journal
- Linux Journal
- Nature

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