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BIOMEDICAL TECHNOLOGY AREA

ANNUAL PROGRESS REPORT (8/1/08 – 7/31/09)

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Contents

General Description of Resource Operation:

The Resource for Macromolecular Modeling and Bioinformatics serves NIH researchers and other scientists through computational tools that serve a wide range of efforts from general analysis of structure and sequence data to advanced experiments combining crystallography and electron microscopy. The Resource advances these tools continuously through a unique interdisciplinary approach that links physical, computational, and biomedical scientists in developing new computational strategies for extremely challenging research applications. The Resource is supported by an outstanding technical staff whose many years of experience and technological contributions make them as highly regarded as the Resource's faculty leaders. Four core development areas focus on (1) structural systems biology, (2) on the development of the general sequence, structure, and modeling tool VMD, (3) on the development of the molecular dynamics program NAMD, and (4) providing a "computational microscope" to support bionanotechnology. The Resource is also active in computational training and operates a popular web site that supports all of its activities, in particular software tool distribution, up-to-date descriptions of ongoing and completed projects, and dissemination of training material.

The Resource is presently engaged in biomedical research at several fronts: battling drug resistance in swine flu, fighting coronary diseases by advancing knowledge on cholesterol uptake by high density lipoproteins and on blood clotting factors, fighting viral infections by resolving the infection process in unprecedented detail, furnishing 4th generation DNA sequencing for personalized medicine. The Resource is also engaged in groundbreaking research at the main frontiers of cell biology, from resolving the folding process of proteins in atomistic detail, to seeing the action of the ribosome in chemical detail, to providing images of how living cells shape their interior forms. Many thousand biomedical scientists from the bench to the world's most advanced computer centers utilize the Resource software every day while high school, college, and graduate students utilize training and visualization material to discover for themselves the miracles of living cells.

The operation of the Resource hinges on its people. Faculty, postdocs, and students from the department of physics, chemistry, and biochemistry engage in the most challenging research problems through collaborations with experimental laboratories, often after contacts from these laboratories. The projects require usually fundamental advances of the available software tools, new algorithmic strategies, and even entirely new theoretical concepts. The physical scientists work closely with computational scientists from the departments of computer science, electrical and computer engineering, and from the NSF National Center for Supercomputing Applications. The team has a long history of close collaboration, in particular, in joint software development that takes advantage of new commodity technologies as well as leading edge technology. The translation into robust, functioning, user friendly software comes about through Resource staff that is in charge of

the actual software, turning requests from application scientists and strategies from computational scientists into modern software code that is continuously adapted to available computational resources of individuals, research groups, and international supercomputing centers. Finally, experienced administrative Resource staff oversees the dissemination of research, software and training materials. On the one hand, the Resource has developed a superbly functioning team, on the other hand the Resource continued to pose for itself every year new challenges stemming from medicine and the adoption of ever new technologies. In the following the operation of the four Resource Cores are summarized.

Structural Systems Biology A key event during the past finding year was the start of a new NSF Center "Physics of Living Cells" that is co-directed by Resource director Klaus Schulten. The aims of the Structural Systems Biology core and of the NSF center largely overlap, except that the NSF center is mainly experimentally oriented. Indeed several research collaborations driving the core's technology development stem from the new center, like ribosome function, protein folding, and whole cell studies. The core technology is advancing in three directions, extending the simulation time scale to the millisecond (presently 50 microseconds have been reached and reported), extending the simulation size scale to 100 million atoms (presently 3 million atom systems have been simulated and reported), and supporting multi-modal microscopies (presently X-ray crystallography and cryo-electron microscopy) to computationally derive structures matching more than one observed modality. On all three fronts progress has been impressive both in regard to the pure technological achievement and in regard to research results reported. To illustrate the latter we list the system-size investigations accomplished, i.e., published or submitted for publication, often through explorations by coarse-grained descriptions followed up by all-atom simulations: tubulation of cellular membranes through lattices of BAR domains; formation of a spherical photosynthetic organelle made up of hundreds of proteins; assembly of lipoprotein-cholesterol-lipid particles; or the structural analysis of a ribosome-translocon complex of 3 million atoms. The core is revolutionizing cell biology in making the team play of macromolecules, e.g., proteins, in cells the subject of systematic modeling studies while pushing the modeling times towards the millisecond, overcoming finally the time scale gap between cell biology and experiment on the one hand and computation on the other hand.

VMD This core develops the software package VMD. The key event during the last year is the recent release of version 1.8.7 that offers a greatly advanced and much expanded package. VMD 1.8.7 includes a full featured, advanced, sequence analysis tool, multiseq, that is completely integrated with the structure analysis part of VMD. The new version sports also a number of plugins for the physical analysis of structures that take advantage of the brand new GPU computing technology, for example for the calculation

of electrostatics. A time-line tool serves the analysis of long and large simulations, simplifying and accelerating an extremely demanding task. Indeed, VMD has become now a program that serves both a general community as well as a community that executes VMD on advanced computer clusters. Lastly, VMD has been upgraded in its graphical rendering abilities, remaining the technology leader in extremely beautiful, yet easy to manage production of images and movies.

NAMD This core develops the software package NAMD. Key events during the past year, that can be reported, are the breaking of the 100 ns / day speed barrier which permits now multi-microsecond simulation times, support of GPU acceleration on a wide range of systems including multi-processor ones, and the further continued tuning of NAMD for 10,000 - 100,000 processor terascale-to-petascale machines. Jointly with VMD, NAMD supports now extremely large simulations of 100 million atom systems and larger ones. NAMD's support of grid forces has been further improved giving researchers greater flexibility in choice of force fields. NAMD has been extended through many features, the most notable one being support of powerful and flexible methods for the‘evaluation of potentials of mean force. A new release of NAMD that incorporates the stated improvements for the widest user community is imminent.

Bionanotechnology Computational modeling is functioning increasingly as a microscope that offers views of structures and processes on the nanoscale where experimental imaging methods cannot be applied. This use is particularly relevant in bionanotechnology where the computational microscope guides the development of nanosensors. An example is the use of nanopores for sequencing DNA, a still elusive goal, but one that is pursued by many. Modeling offers faithful descriptions of nanopores fabricated into silica, silica nitrates, or made of polymers, reproducing well ion conduction properties. The signals produced by biomaterials like DNA can likewise be captured well through modeling, as evidenced through comparison with various observations. Without the movies of processes occurring actually in nanopores and the respective interpretation of measured signals the development of nanopore sensors would be difficult, if not impossible. The core Resource project develops a wide range of tools, not only for imaging wet nanoscale processes involving biomolecules, but also tools for designing naoscale materials and geometries, e.g., pores of various formats, and force fields that permit a unified description of inorganic materials employed in nanotechnology, water, and biomolecule, jointly with electronic sensors integrated into the materials.

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 completed 14 joint publications in the last year through these collaborations, with 11 collaborations with experimental biomedical groups, and three collaborations with theoretical groups. The Resource adds on average one collaboration each month, and completes collaborations in a timely fashion.

Service is provided for the Resource software VMD, NAMD, BioCoRE through responses to user inquiries, support of user groups, maintenance of program libraries, and provision of a visitor and training center as well as an advanced computer laboratory. Downloaders over the last year for VMD increased by 22,000, for NAMD by 5,600, and 905 new users registered for BioCoRE. User support continued, with for example, 4,900 exchanges sent to the VMD support email address. Over the last year 11 visitors received training at the Resources visitor center, and 12 seminars were organized by the Resource. 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, and will maintain an excellent seminar series. The Resource has also overhauled its computational infrastructure, increasing the amount of available data storage on the local network to 160 terabytes.

Training has been and will continue to be available through on-site and online tutorials, case studies, and workshops. In the past year, Resource software developers joined with collaborators from NVIDIA to present a joint tutorial session, "M02: High Performance Computing with CUDA" at the SC08 International Conference for High Performance Computing, Networking, Storage and Analysis, held November 15-17, 2008 in Austin, Texas. Attendance was high with 170 persons in the session, with (98%) of those answering an evaluation survey indicating they would like to see the tutorial session repeated at the next supercomputing conference. To continue its highly successful workshop program, the Resource has over the past year organized, advertised, and is currently registering selected applicants for two hands-on workshops to be held in Summer 2009, on July 6-10 and again on August 10-14 in Champaign, Illinois. Available at the workshops will be two new tutorials posted online by the Resource, the *Membrane Proteins Tutorial* and the *Shape-Based Coarse Graining* tutorial.

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 830,000 unique visitors to its web site, resulting in 2.3 terabytes of information transfer; the visitors downloaded over 24,000 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, 57 talks by Resource PIs and

30 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.

Highlights

Villin Headpiece Folding

All living cells rely on properly functioning proteins to survive and reproduce. Proteins are composed of linear chains of a small set of simple building blocks, and must assume a complex, three-dimensional shape in order to carry out their function; the process of reaching this shape is referred to as protein folding. Understanding the path followed by proteins as they fold is of interest both to allow the design of artifical proteins for specific functions (dictated by their shape) and because it would aid in understanding disorders such as Alzheimer's disease which are caused by the misfolding of proteins. In particular, it is necessary to identify, at the level of individual atoms, the set of shapes assumed by the protein as it proceeds from an initial, unfolded structure to its final, folded conformation.

The challenge of obtaining information on the protein folding process with sufficient detail is so difficult that active research is still underway even for small, well-studied proteins. We have chosen to target one such protein, known as the villin headpiece subdomain (referred to as "villin" for brevity). Several variants of villin have been studied and are known to fold very quickly (in a few microseconds); however, the details of *how* it folds are still unknown. We sought to provide a picture of the villin folding process at the resolution of individual atoms using molecular dynamics simulations; successful unravelling of the villin folding pathway is expected to provide information on principles that will be broadly applicable to the folding of proteins.

Molecular dynamics simulations offer very high resolution views of the structure of biomolecules, such as proteins, over time, but are generally limited by their computational expense to considering processes less than 0.1 microseconds in duration. Recent efforts by the Resource have resulted in substantially improved performance of the molecular dynamics simulation program NAMD [1], such that simulations 10 microseconds in duration can be carried out in a few months on a supercomputer. This improvement in molecular dynamics performance makes it possible to directly compare protein folding simulations with experimental results; experiments, however, cannot provide the detailed picture of folding provided by simulations, and thus molecular dynamics results will provide an unprecedented picture of how villin folding occurs.

Over the last year, scientists at the Resource performed a series of nine simulations of villin headpiece folding.* In addition to successfully reaching the experimentally known structure, the simulations revealed a path through which the protein folds: individual sections of the protein initially form structures similar to their structure in the folded state, but these sections do not properly orient themselves relative to each other [2]. Proper orientation only occurs after a surprising step in which the sections lost their

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

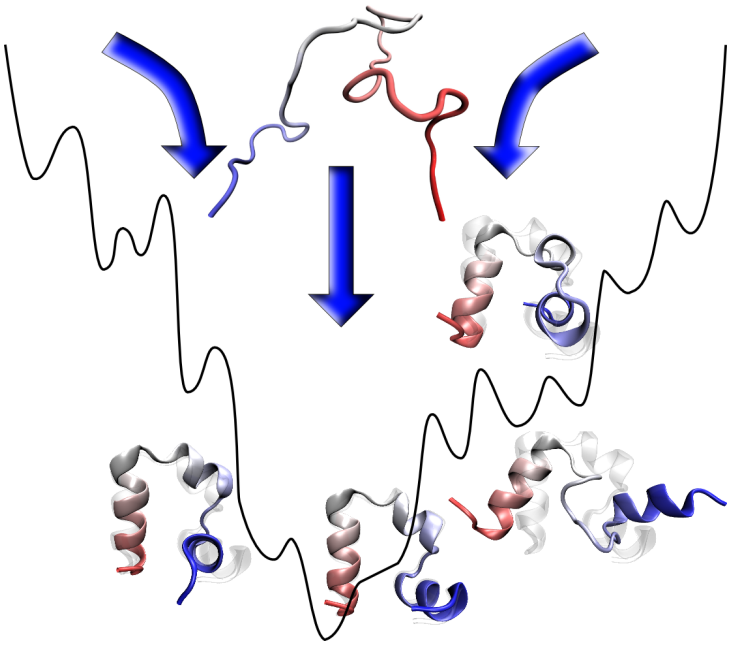

Figure 1: Schematic of the villin folding funnel. A fully unfolded structure is shown at the top, and then several intermediate states occurring during a folding simulation are shown at appropriate points along the funnel, with the folded structure at the bottom.

contact with one another and then quickly come back together to form the folded structure (see Fig. 1). Further simulations on variant forms of villin, which are known to fold even faster, illustrated that the accelerated folding of the variant occurs because interactions which cause the protein to get "stuck" in intermediate states during the folding process have been removed.

The results of the villin folding simulations are in agreement with a long standing theory on protein folding known as the folding funnel hypothesis, and show that proteins fold through a series of stages, with fewer and fewer different shapes available as they approach the final folded structure (*i.e.*, the funnel becomes narrower as the protein goes down it). At the very bottom of the funnel, the proteins must all pass through a common gate (the step in which the structural elements lose contact with each other) and then can reach the final, folded structure. The exact nature of the structures that occured while villin folds, going through stages with correct local structure but incorrect global structure, likely occurs in other proteins as well and will help one to understand how proteins organize themselves as they fold. In addition, the results provide several specific suggestions of how villin folding may be further accelerated through alterations to the protein. Successful experimental testing of these alterations will provide validation for the observed folding mechanism and pave the way for combined experimental/simulation studies on the folding of other proteins.

Membrane Sculpting by BAR Domains

Living cells are characterized by a great diversity of separate internal spaces, the boundaries of which are made of membranes forming convoluted surfaces of manifold shapes. Sculpting such shapes is achieved in many cases by proteins, with a prominent example given by the family of proteins called BAR domains, which drive formation of tubular and spherical membrane structures in cells. BAR domains are found in a great variety of organisms from yeast to humans, and participate in a multitude of cellular processes, such as cell division, cell fusion, endocytosis, and many others [3].

Extensive experimental and computational studies [4–8], including those done by the Resource [6, 8], suggest that BAR domains perform their function by scaffolding a negatively charged membrane with the proteins' curved and positively charged surface. To curve large pieces of membrane, multiple BAR domains have to act in concert, but how this happens has been unclear. A recent cryo-electron microscopy (cryo-EM) study [7] demonstrated that one type of BAR domain, F-BAR domains, form well-organized rows, or spirals, on the surface of membrane tubes that they sculpt. However, many questions remain regarding the molecular mechanisms underlying membrane scaffolding by BAR domains. To characterize membrane sculpting fully, one needs to understand how different types of BAR domains bend membranes, how the arrangement of BAR domains in rows determines the magnitude of the induced membrane curvature, and how BAR domains maintain the arrangements optimal for membrane bending. Experimental studies at present can furnish only static pictures of membrane shapes sculpted by BAR domains [7], obtained after multiple cycles of annealing and freezing, leaving open the question of how the membrane is sculpted dynamically at physiological temperatures.

Resource scientists set out to investigate membrane sculpting by BAR domains computationally, serving as a paradigm system for membrane shaping in cells. However, MD simulations are limited to length and time scales that are insufficient to study the concerted action of multiple BAR domains, which occurs at scales of 100 nm and 100 microseconds. The Resource has therefore developed a four-scale computational approach [6] for studies of multiple BAR domains. The approach employs at the 0.1-nm-resolution level all-atom MD, at the 0.5-nm level residue-based coarse grained (RBCG) MD [9,10] resolving single amino acids and lipid molecules, at the 2.5-nm level shape-based coarse grained (SBCG) MD [11, 12] resolving overall protein and membrane shapes, and at the 12.5-nm level a continuum description based on elasticity theory. The higher resolution descriptions determine and test the lower resolution descriptions, permitting extension of membrane sculpting studies up to 200 microseconds each and 1 ms [8] overall.

The four-scale approach has been employed to study the amphiphysin BAR domain [6,8]. It was found that a single BAR domain produces local membrane curvature with a radius of 10-50 nm, fluctuating within a single simulation and varing between simulations. Mul-

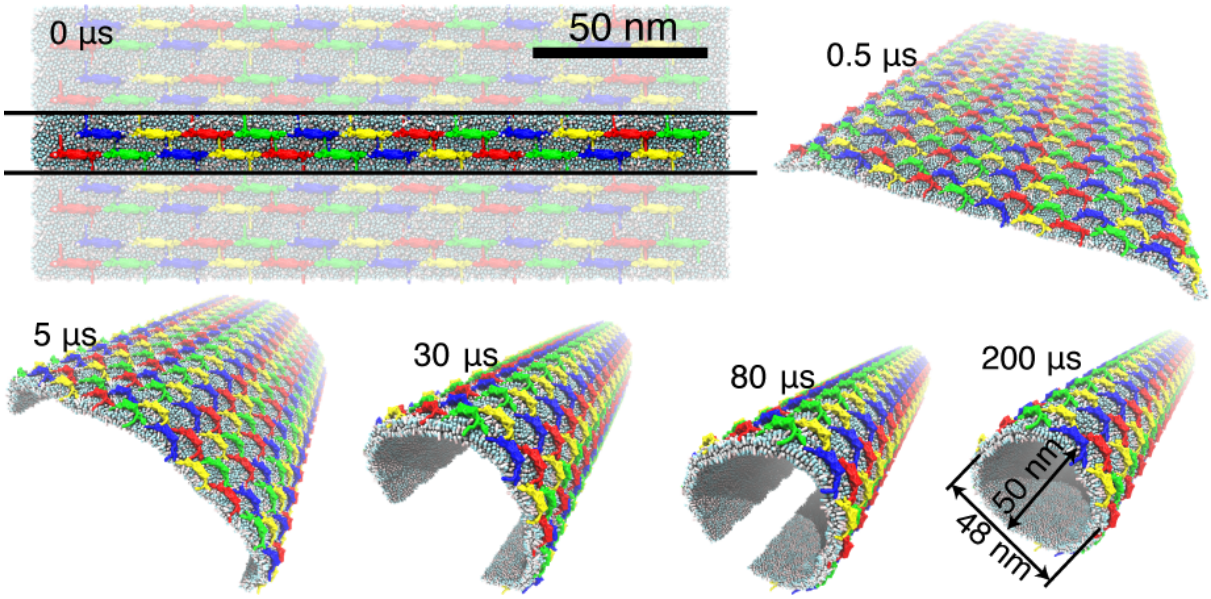

Figure 2: Membrane sculpting by BAR domains observed in simulations [6, 8]. Complete membrane tubulation by a lattice of BAR domains is demonstrated. The starting structure contains a lattice of 24 BAR domains (blue, yellow, red, and green) per unit cell, placed on top of a flat membrane. In the process of the simulation, the scaffolding of the negatively charged membrane by the positively charged, concave surface of BAR domains results in the strong bending. When the edges of the membrane meet and fuse, a complete tube forms. Several periodic images are included to demonstrate formation of a tube.

tiple BAR domains arranged in lattices produce global curvature with a radius varying from 15 to 100 nm depending on lattice type, but remaining stable for a given lattice. Lattice characteristics determining membrane curvature, such as density, orientation, and contacts between BAR domains, were systematically investigated, and several different lattices were found to produce high curvature corresponding to radii of 15-20 nm, in agreement with experimental observations [4]. An extreme all-atom simulation of a particular lattice, involving 2.3 million atoms simulated for over 0.3 microseconds, successfully tested the conclusions drawn from lower-resolution simulations and revealed atomic-level interactions involved in the formation of BAR domain lattices [8]. It was found that the lattices optimal for inducing high membrane curvature are maintained by electrostatic interactions between BAR domains, mediated by well-conserved amino acids.

The Resource also investigated sculpting of complete sub-cellular structures, such as membrane tubes, by lattices of BAR domains. SBCG simulations revealed how BAR domain lattices bend flat membranes into complete tubes [8] on the time scale of hundreds of microseconds (see Fig.2). Thus, all BAR domain simulations together offer a dynamic, molecular-level picture of collective membrane bending by proteins, covering several orders of magnitude of resolution in time and space.

Multiseq

Since the publication of the first draft of the human genome in 2000, bioinformatics data have been accumulating at an overwhelming pace. Currently, millions of sequences and tens of thousands of structures for proteins and nucleic acids (DNA and RNA) are available in public databases. Finding correlations in and between these data to answer critical research questions in terms of sequence and structure changes is extremely challenging. To address this problem, the Resource has developed the MultiSeq [13] [†] extension to its molecular visualization and analysis tool, VMD. MultiSeq provides a unified bioinformatics analysis environment that allows one to organize, display, and analyze both sequence and structure data for proteins and nucleic acids (see Fig. 3). Special emphasis is placed on analyzing the data within the framework of evolutionary biology.

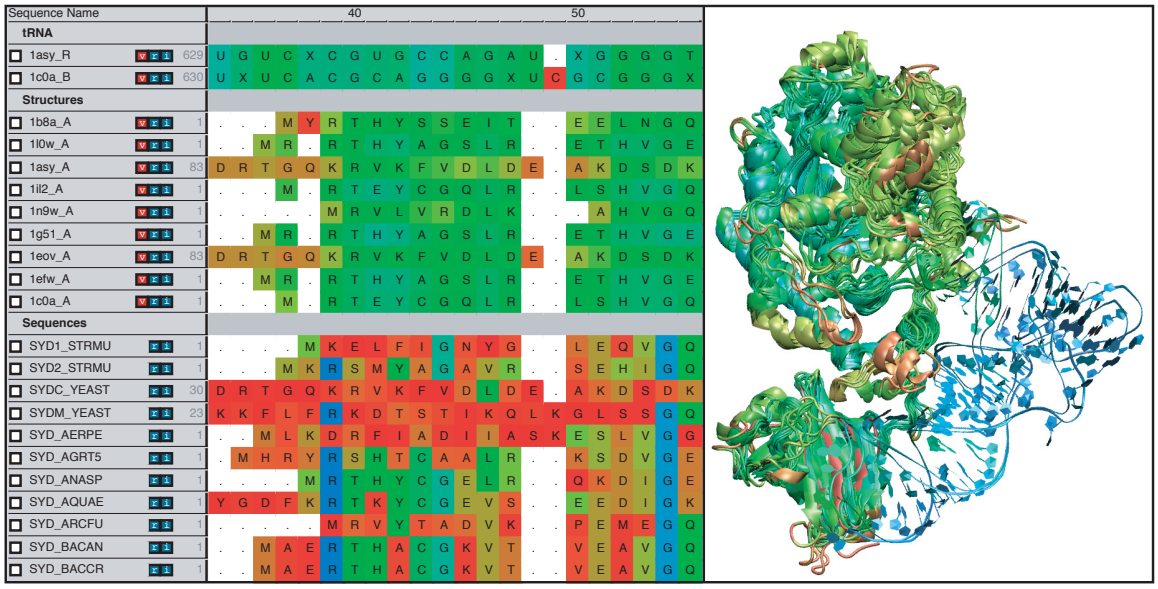

Figure 3: Overview of the MultiSeq environment showing aligned sequence and structural data. (Upper left) 1D representation of structural data colored by structural conservation. (Lower left) 1D representation of sequence data colored by sequence identity. (Right) 3D representation of structural data colored by structural conservation, as shown by VMD. For structural data, the coloring is synchronized between the 1D representation and the 3D representation.

The Resource has released a major new version of the MultiSeq environment this year. Version 3.0 of the software is incorporated into the 1.8.7 release of VMD. Major efforts have been directed toward improving the ability of MultiSeq to handle large data sets,

[†]URL: `http://www.scs.uiuc.edu/~schulten/multiseq/`

and the new version is capable of loading and analyzing on the order of one hundred thousand sequences on a typical desktop machine. Additionally, the Resource has continued to improve the capabilities of MultiSeq to correlate sequences and structures with other source of biological data, including the NCBI taxonomy databases, databases regarding microorganism growth temperatures, and enzyme function databases. All of these enhancements were instrumental during a study of the "signatures" in the ribosome, *i.e.*, the parts of the ribosome that are unique to one of the three domains of life. The ability to analyze large numbers of ribosomal sequences in conjunction with their X-ray structures enabled Resource scientists to map out the evolution of these signatures and estimate their contributions to the tree of life [14].

The capabilities of MultiSeq to jointly analyze sequence and structure data also played a role in a recent study on the recognition of transfer RNA molecules (tRNA) by the protein elongation factor Tu (EF-Tu). EF-Tu transports tRNA molecules to the ribosome during protein synthesis. There are twenty different types of tRNA molecules (one for each of the twenty amino acids), and EF-Tu must bind to each with the correct strength regardless of the type of amino acid carried by the tRNA. Using a combination of molecular dynamics simulation and evolutionary analysis, Resource scientists were able to determine which parts of the protein are responsible for recognition of one particular tRNA, the one carrying the amino acid cysteine [15]. Many of these key regions of the protein are conserved throughout all known life forms.

MultiSeq allows new approaches to be taken in bioinformatic analysis: new relationships can be found and investigated by combining sequence and structure data, and automatic download and use of metadata along with flexible grouping encourages organized analysis of unfamiliar data. MultiSeq extends VMD's capabilities into the realm of sequence based data, and MultiSeq has helped bring widespread use of sequence data to the world of structural biology and vice versa.

Structural Analysis of the Ribosome

The translation of genetic information into proteins is essential for life. In the process of gene expression, genomic DNA is first transcribed into messenger RNA (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 complex molecular machines known, where protein synthesis takes place in every cell. The ribosome is a major target for drug action. Many antibiotics in clinical use block protein synthesis in the bacterial ribosome [16], taking advantage of differences between bacterial and human ribosomes.

The process of the translation of genetic sequences into proteins in the ribosome involves many steps, such as decoding of the genetic information, incorporation of a new amino acid into the protein being synthesized, and movement of the mRNA through the ribosome. During this multi-step process, the ribosome interacts with a number of auxiliary factors and changes its shape, performing different functions along the way. Understanding of each step at the molecular level requires high-resolution structural information of the ribosome at intermediate states of translation. Over the past few years, landmark progress has been made toward obtaining structural data of the ribosome thanks to both cryo-electron microscopy (cryo-EM) and X-ray crystallography. Cryo-EM offers snapshots of the ribosome in functional states, but the current resolution does not allow for determination of the position of each atom from the cryo-EM data. These data are complemented by X-ray crystallography, which provides atomic resolution for most of the ribosome. However, the X-ray structures usually do not represent functional intermediates of the ribosome, due to the typically non-natural crystallization conditions. Hybrid methods are needed to combine structural information from cryo-EM and X-ray crystallography, furnishing atomic models of intermediate states of the ribosome throughout its functional cycle [17].

The Resource developed a novel computational method, molecular dynamics flexible fitting (MDFF) [18,19], to combine cryo-EM and X-ray data.[‡] MDFF incorporates cryo-EM data into molecular dynamics simulations, flexibly fitting atomic structure into cryo-EM density maps. MDFF is based on two programs developed by the Resource, VMD [20] and NAMD [1]. MDFF has been successfuly applied to the study of the ribosome [21], as well as protein-induced membrane curvature [22, 23]. Resource scientists collaborate with several leading EM laboratories, which are applying MDFF to different systems and driving further development of the method.

In collaboration with Joachim Frank (Columbia U., HHMI), a leader in structural analysis of the ribosome by cryo-EM, Resource scientists applied MDFF to obtain an atomic model of the ribosome at a key step in translation, namely the delivery of a new amino acid

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

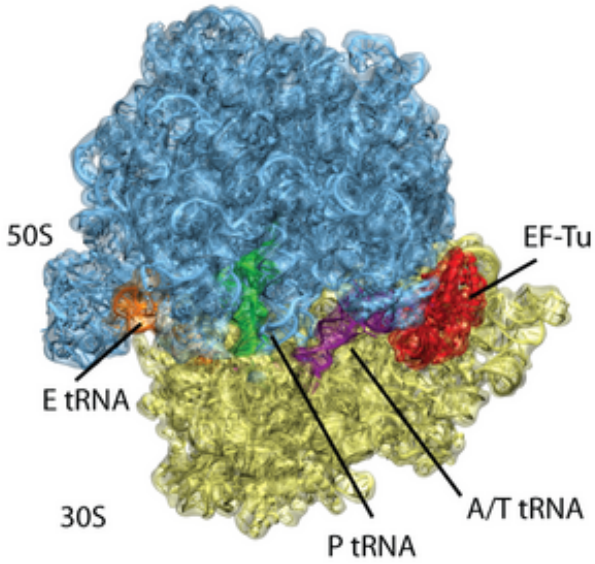

Figure 4: Atomic model of the ribosome bound to factors derived from a 6.7-Å EM map. The EM data is shown in transparent surface, with atomic model generated with MDFF showed in cartoon.

to the ribosome (Fig. 4).[§] Each amino acid is delivered to the ribosome in the form of a complex between elongation factor Tu (EF-Tu), a transfer RNA (tRNA) carrying the incoming amino acid, and GTP. EF-Tu plays a critical role in establishing the fidelity of translation: only if the incoming tRNA matches the message in the mRNA does EF-Tu hydrolyze GTP into GDP, permitting translation to move forward. Using the obtained atomic model, Resource scientists were able to determine the mechanism by which the ribosome induces the correct shape in EF-Tu that leads to GTP hydrolysis. The mechanism involves opening of a gate formed by two EF-Tu amino acid residues, allowing the critical residue histidine 84 access to GTP, which leads to hydrolysis [21].

The results described above are just a glimpse of what can be done by combining cryo-EM and X-ray data using MDFF. Several other steps of translation are under investigation by Resource scientists, such as the control of mRNA movement through the ribosome, regulation of translation by certain nascent proteins, exit of the tRNA from the ribosome, and a quality control mechanism that enhances the fidelity of translation. Structural analyses using cryo-EM and X-ray data are being complemented by large scale molecular dynamics simulations, allowing Resource scientists to state and test hypotheses regarding several aspects of ribosome function. Investigating key steps in translation at the molecular level is of major interest to understanding the molecular biology of the cell. Furthermore, atomic models of intermediate states of translation provide new targets of antibiotics, which are desperately needed due to the constant emergence of antibiotic-resistant pathogenic bacteria.

[§]URL: http://www.ks.uiuc.edu/Research/ribosome

Acceleration of Biomolecular Simulation, Analysis, and Visualization with Graphics Processing Units

Over the last several years graphics processing units (GPUs) incorporated in personal computers have grown far beyond their original intended purpose and have become programmable computing devices capable of performing trillions of floating-point arithmetic operations per second. The Resource has begun to exploit GPUs for a revolutionary increase in biomedical computing power for biomolecular simulation, analysis, and visualization. The outcome of this effort, which is already well underway (first publication in 2007) and ahead of other similar efforts, promises to bring the power of compute clusters to presently available laptops and to accelerate supercomputer calculations, as carried out by many NIH investigators, by a factor of 10 times or more[¶]. GPUs have achieved significant penetration into the scientific computing community since the release of the CUDA programming system in 2007 by NVIDIA, a key GPU manufacturer with whom the Resource collaborates closely.

Several new GPU-accelerated analysis algorithms have been added to the Resource's molecular visualization and analysis tool VMD[‖], increasing performance for computationally demanding tasks such as calculation of electrostatic fields [24–26]. The GPU-accelerated analysis algorithms enable calculations that would have previously required a cluster of 50 or more traditional processor (i.e., CPU) cores to be performed on a single desktop computer containing one or more GPUs, making these capababilities accessible to researchers that lack the technical expertise to use cluster-based solutions and lowering the equipment costs required to do these calculations.

Many biomedical research projects rely on quantum chemistry calculations and there is high demand for the integration of the visualization of molecular orbitals and quantum chemical properties with large and complex models of biomolecules. The computations needed for the display of electron dynamics in large biomolecules are too expensive to allow interactive visualization at present. GPUs pose an opportunity for achieving the required speedup. The Resource has developed a functional prototype for the GPU-accelerated calculation of molecular orbitals, enabling interactive animation [27]. The key innovation is the ability to perform these calculations in fractions of a second, a hundred times faster than other tools.

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

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

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

Figure 5: High-performance computing cluster with 64 graphics processors.

upgraded its existing GPU cluster. The Resource was able to demonstrate a factor of twelve overall speedup from GPU acceleration when running a million-atom NAMD** simulation on the entire cluster, performance equivalent to hundreds of traditional processors [28].

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

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Subprojects

BTA UNIT: T

TITLE: Scalable Molecular Dynamics Software NAMD

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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 [1,2]. NAMD employs the prioritized message-driven execution capabilities of the Charm++/Converse parallel runtime system (http://charm.cs.uiuc.ed allowing excellent parallel scaling on both massively parallel supercomputers and commodity workstation clusters. NAMD is distributed free of charge to over 30,000 registered users as both source code and convenient precompiled binaries. 6000 users have downloaded multiple releases. NAMD 2.7b1 was released in March 2009 and in the six weeks since its release has been downloaded by over 1,300 users, 200 of whom are NIH-funded.

NAMD 2.7b1 incorporates significant parallel scaling enhancements, including a two-dimensional decomposition of the particle-mesh Ewald method, improved message prioritization, optimized communication for the Blue Gene toroidal network, and a new topology-aware load balancer. Serial performance has been increased via specialized constraint and pairlist routines for x86 processors. This release also includes preliminary support for graphics processor acceleration based on the CUDA technology from NVIDIA [3, 4], which will be fully deployed in NAMD 2.7b2.

Free energy calculations have been greatly extended and updated in NAMD 2.7b1, resulting in great increases in accuracy and efficiency. An arbitrary number of collective variables may be defined for multidimensional analyses and biased simulations. Free-energy surfaces or potentials of mean force (PMF) can be constructed

using a variety of methods, which currently include meta-dynamics, the adaptive biasing force (ABF) method, umbrella sampling and steered molecular dynamics (SMD). Both free energy peturbation (FEP) and thermodynamic integration (TI) methods for alchemical transformations are now implemented including soft-core correction to circumvent singularities in the van der Waals potential.

NAMD 2.7b1 provides the ability to define external potentials discretized on multiple, finite grids. The user can arbitrarily select a subset of atoms onto which these potentials act, which, for instance, can be utilized in the context of mean-field descriptions of the environment. One important application is molecular dynamics flexible fitting (MDFF), which allows the user to fit high-resolution structures into volumetric, low-resolution density maps to reconcile crystallographic and electron microscopy data. MDFF also relies on the new NAMD capability of defining arbitrary bonded terms to constrain secondary structure during the fitting process.

New simulation features in development include coarse-grained models, both fluctuating charge and Drude polarization models, and interfaces to quantum chemistry codes for quantum/classical simulations. A new compressed molecular data structure allows very large simulations to be run on platforms with limited memory per node, and combined with new parallel input and output routines has allowed test runs of a 100-million-atom benchmark simulation for the NSF Blue Waters petascale machine to be installed at Illinois.

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TITLE: NAMD-Lite and Molecular 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 the Resource in using GPUs (graphics processing units) to accelerate the computation of electrostatics. The multilevel summation method, implemented in NAMD-Lite, offers fast electrostatic evaluation for both periodic and nonperiodic boundary conditions [1, 2]. The previously reported efforts included the GPU acceleration of the short-range part of multilevel summation [3] and its application to ionization of a molecular system and calculation of time-averaged potentials. More recent work has improved the GPU acceleration of the short-range part [4] and has also applied GPUs to the long-range part of multilevel summation [5], enabling the computation of a high-resolution map of the electrostatic potential for a system of 1.5 million atoms in under 12 seconds. The new multilevel summation implementation has now been integrated into VMD [6] (http://www.ks.uiuc.edu/Research/vmd/). Continuing efforts include GPU acceleration of the atomic forces calculated by multilevel summation, along with a distributed memory parallelization for incorporation into NAMD [7] (http://www.ks.uiuc.edu/Research/namd/).

The Resource has made progress in implementing models for polarizable force fields in NAMD-Lite and NAMD. Polarizable force fields improve accuracy of biomolecular simulation by modeling electron density response to an electric field. The Resource is collaborating with Dr. Roux, U. Chicago, to support a polarizable force field based on classical Drude oscillators [8]. Development of the Drude model is complete in NAMD-Lite. NAMD now supports the five-point water model [9] using a novel dual-temperature Langevin thermostat for dynamic simulation of the Drude oscillators, an approach that offers superior parallel scalability over the methods previously investigated [10]. Work is underway to finish NAMD support for all aspects of the Drude model. The Resource is also implementing the fluctuating charge model for polarization [11, 12] in collaboration with the Brooks's NIH Resource Center for Multiscale Modeling Tools in Structural Biology. NAMD now supports the four-point fluctuating charge water model, and work is ongoing toward full support for fluctuating charge polarization.

The NAMD-Lite framework has been used to develop the new VMD plugin EnergyTool (previously named NLEnergy) that calculates energies and forces on VMD atom selections and performs energy minimization. The features provided by EnergyTool will be used by the ParaTool plugin for force field parameterization. The EnergyTool interface drives the supporting data structures and force evaluation routines in NAMD-Lite, enabling efficient updates to the force field parameters and topological structure of a molecular system with repeated evaluation of its potential energy and forces, which is needed for use by ParaTool.

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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 new GPU-accelerated algorithms for the computation of three-dimensional electrostatic potential maps surrounding the biomolecules. Speedups have been exhibited up to a factor of 26 relative to state-of-the-art CPUs, enabling with three GPUs the computation of a high-resolution map for a system of 1.5 million atoms in under 12 seconds [1,2]. These algorithms have subsequently been incorporated into VMD [3], the molecular visualization and analysis package developed by the Resource.

GPU acceleration techniques have also recently been applied to NAMD [4], the parallel molecular dynamics package developed by the Resource. In molecular dynamics simulations, the majority of computational work is spent on evaluating the forces between atoms that are not chemically bonded. The use of GPUs has been shown to accelerate this force calculation by a factor of twelve over state-of-the-art CPUs, and can be deployed on GPU-accelerated computing clusters with good scaling performance [5].

The Resource recently developed a new algorithm for accelerating the visualization of molecular orbitals through the use of GPU computing [6]. The early prototype implementation has achieved hundred-fold speedups over conventional CPU-based processing, enabling for the first time the ability to compute molecular orbitals from wave function data on-the-fly at an interactive rate. This development promises to enable visualization of dynamics for quantum chemistry simulations, and will serve as the basis for visualization of other quantum chemistry properties.

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

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ABSTRACT: VMD [1] 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 with many new features and has been tuned to provide higher compuational and graphical performance. The Windows version of VMD now takes advantage of multicore CPUs, enabling significant performance increases when rendering complex scenes or working with large structures. Many new GPU-accelerated algorithms have been added to VMD to increase performance for computationally demanding tasks such as calculation of electrostatic fields [2–4], and computation and display of molecular orbitals for visualization of quantum chemistry simulations [5]. New plugin interfaces have been developed to allow VMD to read simulation log files from quantum chemistry packages such as GAMESS and Gaussian. The quantum chemistry data can be used for graphical display of the simulated structure, and can be accessed via scripting interfaces. VMD has recently been updated with support for version 8.5.6 of the Tcl scripting language. An updated version of the multiple sequence analysis plugin has been incorporated into VMD, greatly increasing performance and usability when processing large batches of sequences.

Over 50,000 users have registered for VMD 1.8.6 since it was released on April 7, 2007. Alpha and beta test versions of VMD 1.8.7 have been made available over the past 12 months in order to allow users to test new features and give feedback to the VMD developers.

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TITLE: MultiSeq: Sequence and Structure Analysis Software

KEYWORDS: sequence, structure, software

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ABSTRACT: MultiSeq [1] (http://www.scs.uiuc.edu/~schulten/multiseq/) is a unified bioinformatics analysis environment within VMD that allows one to organize, display, and analyze both sequence and structure data for proteins and nucleic acids. Special emphasis is placed on analyzing the data within the framework of evolutionary biology.

The Resource has released a major new version of the MultiSeq environment this year. Version 3.0 of the software is incorporated into the 1.8.7 release of VMD and the new version is capable of working with much larger datasets and supports

new databases such as the Prokaryotic Growth Temperature Database and taxonomic information for sequences from the Comparative RNA website. Support for PSIPRED secondary structure prediction has been added, and the QR algorithm can now be used with nucleic acid sequences. Numerous graphical display elements have been inproved, and initial scripting support has been added for the MultiSeq procedures.

In the next year the Resource will continue to refine MultiSeq and add additional features to allow biomedical researchers to combine sequence and structure data.

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BTA UNIT: T

TITLE: Timeline: Trajectory Analysis and Event Identification in VMD

KEYWORDS: software, structural systems biology, petascale, data visualization

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ABSTRACT: ABSTRACT

A key part of the process of analyzing an MD trajectory is identifying important events. This traditionally requires a scientist to spend many hours reviewing animated structures, examining different regions of a large simulated system, and calculating appropriate geometric, statistical, and other properties. A more productive use of a scientist's time is to use a "whole-trajectory" view, produced by performing analysis calculations for every frame of a trajectory, and for each small component of the entire simulated structure – for example, calculating the secondary structure of every residue of a protein, and for every frame of a trajectory. The 2D plot that results allows quick identification of events that take place throughout the trajectory. With the move to petascale computation, such analysis is increasingly necessary: as system sizes, time scales, and trajectory counts grow, the time required to manually review animated structures becomes impractical, while the time required to asses a static whole-trajectory plot remains the same.

The Timeline software we have developed provides a whole-trajectory 2D raster plot (time vs. structure vs. property) calculated using using one of the set of common analysis methods provided, or with user-defined algorithms / analysis results data. Timeline is interactively connected to the 3D molecular structure displayed in VMD; a click on the 2D plot highlights the appropriate structure at the appropriate time step in the 3D structure view, and vice versa. Large additions have been made to the software during the last funding period: group analysis for analyzing entities like hydrogen bonds and salt bridges, an interface

for pre-computed analyses and user-defined functions, new statistical and geometrical analyses, new user-interface features to better deal with large systems, plus general robustness/software-infrastructure improvements. Switching among several pre-computed analysis sets allows usable interactive performance with large systems and long trajectories.

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ABSTRACT: Many biomedical research projects rely on quantum chemistry calculations as well as on molecular dynamics simulations. There is high demand for the integration of the visualization of molecular orbitals and quantum chemical properties with large and complex classical models. Such a tool would enable entirely new ways of displaying multimodal simulation results. Existing tools for quantum chemistry visualization are incapable of displaying structural dynamics of large biomolecular complexes. Furthermore, the computation needed for the display of molecular orbitals can take seconds to minutes on CPUs, even for small molecules, preventing the display of electron dynamics at interactive speed (20 frames per second). GPUs pose a great opportunity for achieving the required speedup. Supporting interactive animation of the dynamics of molecular orbitals and quantum chemical properties (e.g. spin-densities, molecular electrostatic potential) will open the door to a new era of quantum chemistry visualization. Orbital dynamics allows one to develop a much better intuition about the participation of electrons in chemical reactions which is key to understanding biochemical reaction mechanisms.

We have developed a running prototype for the GPU-accelerated calculation of molecular orbitals, enabling interactive animation [1]. Our innovation here is the ability to perform these calculations in just fractions of a second (this compared to

minutes with other tools). The prototype implementation already achieves a factor of 100 speedup compared to our efficient CPU implementation, but we expect to improve efficiency further. Due to algorithmic similarity, our approach for computing molecular orbitals serves as a template for the GPU-accelerated calculation of other quantum chemical properties.

We have already implemented a general interface to quantum chemistry simulations in VMD that allows users to develop plugins for reading the results of any quantum chemistry calculation with minimal effort. All standard data from the calculations can be read and stored by VMD and can be processed arbitrarily by the user through VMD's scripting interface. The display of quantum chemistry data can be combined with any of VMD's other graphical representations, e.g., can be superimposed on standard structure data. Together with the proposed GPU-based animation of quantum chemistry data the existing framework will turn VMD into an unprecedented molecular visualization program.

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BTA UNIT: C

TITLE: MDFF Development

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

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ABSTRACT: Cryo-electron microscopy provides density maps of biomolecular complexes in their functional states, but only at low resolution, unlike X-ray crystallography, which provides atomic-resolution structures of biomolecules but usually not in a physiological state. Computational methods to combine information from both techniques hold the promise of generating physiologically accurate, high-resolution structures of biomolecular complexes. To combine experimental data from these two sources, the Resource developed a novel method, molecular dynamics flexible fitting (MDFF; http://www.ks.uiuc.edu/Research/mdff) [1,2], to fit atomic structures into cryo-EM density maps. MDFF employs molecular dynamics (MD) to perform the fitting, which allows flexibility while maintaining a realistic conformation. The standard MD force field is modified by incorporating the EM density map as an attractive potential that drives atoms into high-density regions. Furthermore, restraints are

applied to preserve secondary structure of the biomolecules. MDFF setup and analysis are performed with the Resource's molecular visualization program, VMD, and MDFF simulations are conducted using the Resource's MD simulation software, NAMD. Since NAMD is highly scalable and supports simulation of large systems, MDFF can be applied to large macromolecular complexes such as the ribosome [3].

Several tools have been developed to assist researchers in setting up, running, and analyzing MDFF simulations. Many of these tools are packaged together as plugins for VMD. The MDFF VMD plugin includes tools to convert cryo-EM density maps for use as simulation input, as well as a tool to calculate a predicted cryo-EM map from a molecular model produced by the simulation, to allow direct comparison of simulated and experimental results. The Volutil VMD plugin provides volumetric map manipulation capabilities, as well as file format conversion. The SSrestraints VMD plugin automates the generation of secondary structure restraints required by MDFF. The simulation program, NAMD, includes a feature for applying grid-based potentials to the atoms in a simulation [4], allowing the EM density map potential to drive the simulated structure toward the observed physiological state. This grid-based potential feature has recently been improved to allow larger, higher-resolution cryo-EM maps to be used on computers with limited memory.

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BTA UNIT: C

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 have benefited greatly from the increased allocations of computational resources from the National Science Foundation (NSF) funded National Supercomputing Centers. The total number of Service Units awarded to the Resource by NFS's Large Resource Allocations Committee has increased to 30.3 million service units compared to 20.4 million from last year. The Resource has also been awarded 5 million service units 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 will be upgrading its 8-node graphics processing (GPU) cluster with Nvidia Tesla C1060 processing cards. This upgrade will allow for greater computational capacity increasing the utility of the cluster. This will bolster the Resource's continuing efforts in developing GPU-accelerated versions of the NAMD (http://www.ks.uiuc.edu/Research/namd/) and VMD (http://www.ks.uiuc.edu/Resear packages distributed by the Resource. Support for the general software development

and testing activities of the Resource has been improved with 4 high resolution displays on public graphical workstations and 4 additional Apple Mac Book Pro laptops with advanced graphics systems allowing for computation and molecular graphics.

The increase in available compute power has required a shift of the investments in hardware and services of the Resource computational facility. The Resource has supplemented its local computational capabilities with the purchase of a large memory 16 core Sun X4600 server. This server was outfitted last year with 128 GB of Random Access Memory (RAM) and a 9 TB hard disk array for large memory computation. The Resource will be doubling its memory to 256 GB this year. Additionally, the purchase of a Sun Ultra 40M2 workstation with upgraded memory and graphics has enabled the Resource to bolster its visualization facility. This coupled with our existing visualization setup has allowed for greater use of stereoscopic visualization for the Resource. As of last year, the Resource had 112 TB of available data storage on its local network. This has been increased to 160 TB with the purchase of another Sun X4500 server boasting 48 1 TB hard drives capable of serving data directly to the entire network. Additionally, the Resource has purchased 2 Sun X4200 servers each with 9 TB of hard drive space to replace older file servers used for day-to-day operations. This space will be backed up using a new backup system currently being installed. All of the mentioned servers utilize the ZFS file system allowing for greater flexibility and simplified administration.

BTA UNIT: C

TITLE: Developing Nanopores as Nanosensors

KEYWORDS: nanopore, DNA sequencing, genotyping, human genome, force spectroscopy, silicon, silica, ionic conduction, polymer nanopore, 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 [1], but can also be artificially manufactured in silicon-based membranes [2] and polymer wafers [3]. 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. There are many promising applications for nanopores; for instance, developing a DNA sequencing technique or building nanofluidic devices. The Resource is working in close collaboration with experimentalists (Gregory Timp UIUC, Zuzanna Siwy UCI) and theoreticians (Jean-Pierre Leburton UIUC, Thorsten Ritz UCI) to understand the physics of synthetic nanopores and improve their usability as sensors. Atomic-scale modeling was carried out in the following directions: (i) translocating DNA-protein complexes through nanopores; (ii) stretching/unzipping DNA hairpins with a nanopore; (iii) sensing DNA sequence with a nanopore capacitor and (iv) modeling of ion interactions inside nanopores.

(i) Restriction endonucleases selectively bind to specific DNA sequences and in the presence of cofactors, cleave double-stranded DNA. The Resource's collaborator Dr. Timp discovered that, in the absence of cofactors, restrictions enzymes in conjunction with nanopores can be used to quickly recognize single-nucleotide polymorphism (DNA mutations) in the segment of interest. In a joint-publication with Prof. Timp's group, we have previously shown that there is a voltage threshold at which the enzyme EcoRI separates from the DNA [4]. In a second study, we now show that the threshold depends on the DNA sequence at the recognition site and is independent of the pore geometry [5]. Relying on the the high sequence specificity of restriction endonucleases, we can use nanopores to differentiate DNA sequences that differ by only one base mutation at the recognition sequence.

(ii) Similar to the DNA-enzyme work described above, a threshold voltage was observed in experiments for translocation of a hairpin DNA (hpDNA) through silicon-nitride nanopores, which depends on the diameter and the secondary structure of the DNA [6]. This initial discovery was further studied in a second joint-publication with Prof. Timp's group [7]. We found that for synthetic pores, the hpDNA can translocate via three modes: unzipping of the double helix and in two distinct

orientation streching/distortion of the double helix. Furthermore, we showed how the presence of hpDNA affects ionic current measurements. In experiments and simulations, the ionic current relative measurements in the absence of DNA can either drop below 10% or rise beyond 200%. In simulations, we observed that the fluctuation on ionic current are related to different DNA conformations in the pore.

(iii) 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. 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. Such hysteresis is sequence specific and may produce detectable sequence-specific signals [8].

(iv) 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 studied the rectification of ionic current on silica nanopores, i.e., where ionic current measurements are higher for one voltage polarity than for the opposite polarity, producing an asymmetric current-voltage (I-V) curve. Our results indicate that ion-binding sites at the silica surfaces are responsible for the rectification effect [9]. Furthermore, we studied how ions interact with DNA free in solution [10] and inside a nanopore [11]. Finally, we also studied the dynamics of monovalent and divalent cations inside polymeric nanopores, showing that the ion adsorption of divalent cations change the transport properties [12].

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BTA UNIT: C

TITLE: Physical Properties of Methylated DNA

KEYWORDS: metylation, DNA, epigenetics, nanopore, force spectroscopy, DNA mechanics

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ABSTRACT: Cytosine methylation (http://www.ks.uiuc.edu/Research/methylation/) is a chemical modification on DNA, which involves replacing a hydrogen atom by a methyl group at the 5' position in cytosine. Methylation of DNA is one of the most important mechanisms in epigenetics. Without changing the sequence of DNA, methylation can alter the expression levels of genes [1]. The physical mechanism underlying methylation is presently under intense study, yet current measurement methods for methylation profiles are still lacking. Previous experiments suggest that methylation can affect DNA properties by changing its structure or its dynamics [2, 3].

The Resource is working in close collaboration with Electrical Engineer (G. Timp) and Biological Physicist (H. Gaub), both of whom are experts in single molecule sensors, to elucidate the structural and dynamic properties of methylated DNA as well as develop new detection methods for DNA methylation. Two atomic scale modeling experiments were carried out to complement two single molecule experiments: (i) detecting 5'-methylcytosines on DNA with synthetic nanopores and (ii) differential double strand rupture measurements. For study (i), the effect of methylation of DNA was studied computationally by driving negatively charged DNA molecules through a synthetic nanopore by means of electric fields [4–6]. Simulations revealed a difference in nanopore permeation between methylated DNA and un-methylated DNA [7]. In study (ii), simulations of stretching and unzipping double strands of methylated and un-methylated DNA were carried out; they showed that methylated DNA is more stable than un-methylated DNA. Both sets of simulations not only agreed well with their respective experimental observations, but also showed in atomic level detail the reasons for the differences in the mechanical properties of methylated and un-methylated DNA.

In study (i), experimental measurements showed that the voltage threshold for permeation through a nanopore of methylated DNA is lower than that of un-methylated DNA [7]. Consistent with this, simulations showed a significant difference between nanopore translocation speeds of methylated and un-methylated DNA at a 4 V bias; these were 1.0 nm/ns and 0.8 nm/ns, respectively. This demonstrates that methylated DNA passes through the nanopore more readily than un-methylated DNA. These simulations also revealed that the structure of DNA inside the nanopore is more ordered for methylated than for un-methylated DNA [7]. In study (ii), the simulations revealed that methylated DNA develops less faults in stretched, i.e., S-form, double strands than un-methylated DNA; this difference results from double strands of methylated DNA being harder to separate than those of un-methylated DNA. These studies suggest that methylation stabilizes DNA mechanically, e.g., rendering DNA less prone to structural fluctuations. A reduction in structural fluctuations could readily translate into different transcription levels. The relationship between stability and transcription level is an important insight into this fundamental mechanism of epigenetics.

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BTA UNIT: C

TITLE: Maturation of High-Density Lipoproteins

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

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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 [1].

Two X-ray crystal structures of lipid-free apo A-I have been determined [2,3]; 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 [4]. 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 [5]. The Resource utilizes these homogeneous and well-characterized nanodisc particles [6, 7] in molecular dynamics studies [8–12].

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 [9–15].

Previous simulations have revealed the full assembly path of nanodiscs starting from a randomized distribution of lipid, protein, and water, to form discoidal HDL particles [10, 11]. Recent simulations have focused on the dynamics of HDL maturation [16]. Coarse-grained simulations were used to transition a discoidal HDL to a spherical HDL particle by allowing the HDL particle to absorb cholesterol ester molecules and to form a hydrophobic core. The resulting mature spherical HDL particle was reverse coarse-grained [12] into an all-atom representation and further equilibrated. This all-atom description of a spherical HDL particle revealed an ideal location for the binding of lecithin cholesterol acyltransferase, the key enzyme that converts cholesterol to cholesterol ester during HDL maturation.

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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 [1]. However, being able to enhance recognition and passage across the membrane could increase yields for artificially created proteins such as insulin [2]. 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.

In the past year, Resource investigators determined the individual functions of the pore ring and plug by simulating two mutants in which half or all of the plug is deleted, both crystallized by Resource collaborator Tom Rapoport [3]. The structures showed that new plugs form from the remaining residues and that the channel remains closed; electrophysiology experiments, however, indicated that the mutant channels fluctuate between open and closed states [4]. Extensive simulations of the large (100,000-atom) system totaling over 0.35 microseconds revealed why the mutants permit conduction but the native channel remains closed [5]. 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. The results expand on the model for channel gating by explaining how destabilization of the plug can lead to channel opening.

More recently, studies of the translocon have taken advantage of the Resource's work on the ribosome, a driving project of the structural systems biology core of the Resource, 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 [7]. After fitting, water, membrane, and ions were added to the system using VMD, resulting in a system composed of 2.7 million atoms. Simulation of this system requires use of the latest memory optimized version of NAMD. Simulations of the ribosome-translocon complex illustrate the specific interactions between ribosome and translocon that maintain the complex [8]. These interactions are all found to occur in conserved regions of the translocon.

Furthermore, the presence of the ribosome destabilizes the plug of the translocon, preparing it for translocation. Modeling and simulation of a ribosome in complex with a back-to-back translocon dimer demonstrate that the presence of the dimer enhances both the stability of the complex and binding of the ribosome to the first copy of the translocon. The increased stability of the complex explains why oligomers of the translocon may be required for translocation, despite the fact that only one copy serves as the active channel.

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BTA UNIT: C

TITLE: Voltage-gating Mechanism of Potassium Channels

KEYWORDS: K channel, shaker, voltage-gating, ion channels, membrane proteins

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ABSTRACT: Voltage-gated potassium (Kv) channels (http://www.ks.uiuc.edu/Research/kvchannel/) are integral membrane proteins present in all three domains of life. In a specialized class of animal cell, known as excitable cells - including neurons, muscle cells, and endocrine cells - Kv channels work with other cation channels (sodium and calcium channels) to regulate the electrical activity and signaling of the cell [1]. Kv channels activate (open and close) in response to changes in the electrical potential across the cell membrane allowing passive and selective conduction of K+ ions through the channel. Potassium conduction is directed by the electrochemical gradient across the cell membrane and can achieve very high rates, while still discriminating against all other cations (including the smaller Na+ ions) [1]. In addition to electrical signaling in nervous systems, Kv channels play an important role in the regulation of cardiac excitability and regulation of insulin release. In humans, malfunction of

these channels can result in neurological or cardiovascular diseases such as long QT syndrome or episodic ataxia [2].

The crystal structures of Kv1.2 [3, 4], a member of the Shaker K+ channel family, have provided the first view of the molecular architecture of a mammalian potassium channel in a putative open state at 3.9 Å resolution. However, the structure of the channel in the closed state is still unknown.

In collaboration with the Yarov-Yarovoy and Roux labs, the Resource has developed an atomic model for the closed state of the channel. The initial model was generated using the structure prediction program ROSETTA [5, 6]. The open and closed state models of the channel [7] were refined in several stages of molecular dynamics simulation. Each model was simulated in explicit water/membrane environment in the presence of an electric field. A total of 400ns of simulations were required to obtain stable conformations of the channel, for the systems containing 100,000 or 350,000 atoms.

To study the gating mechanism of Kv1.2, the gating charge that is transferred across the membrane upon activation of the channel is calculated from 900 ns of all-atom MD simulation of the two protein states. The contribution of individual charged residues of the channel to the total gating charge is determined, showing that positions of four conserved arginines within the transmembrane region are tightly coupled to the membrane voltage, and that their movement drives the transition of the channel between the two states. The results are in agreement with experimental values obtained for the gating charge [8,9], indicating that the refined models of Kv1.2 are representatives of the two functional states of Kv channels.

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BTA UNIT: T

TITLE: Molecular Dynamics Simulations of Protein Folding

KEYWORDS: Protein folding, villin headpiece, WW domain, structure prediction

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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 simulations that are tens of microseconds or longer in duration, periods which until recently were unattainable through simulation. However, thanks to advances in parallel molecular dynamics simulations, the full folding process of small proteins can now be studied computationally (http://www.ks.uiuc.edu/Research/folding).

The Resource is currently involved in a series of protein folding projects, focusing on three small proteins experimentally known to fold in ten microseconds or less: the Pin1 WW domain, the villin headpiece subdomain, and the lambda repressor. Complementary experimental studies on the folding processes of these proteins, and testing of predictions of mutations to alter the folding rate made by the Resource, are being performed in the laboratory of collaborator Martin Gruebele. Simulation of each of the target proteins in explicit solvent requires a system containing 30,000-40,000 atoms, and must be 5-10 microseconds in duration to observe complete folding events. The necessary simulation timescales can be obtained only using the molecular dynamics program NAMD [1], which has been optimized to deliver

performance of 100 ns per day on the folding systems [2], a tenfold improvement over performance prior to optimization.

A total of nine folding simulations were performed on villin headpiece, including both the wild type protein and a fast-folding mutant. The wild type protein folded to a native state reliably, and the simulations showed a single, consistent mechanism for the final stages of folding, in which the rate limiting step involved dissociation of the secondary structure elements from each other to allow a shift from incorrect to correct relative orientations [3]. The fast folding mutant, in contrast, was observed to fold quickly in some trajectories but not at all in others; however, the values of the experimental observable used to measure folding reached native-like values quickly even in the trajectories that misfolded, suggesting that a new experimental metric is needed. Several alternative metrics were suggested based on the results of the folding simulations which should properly discriminate between misfolded and folded conformations [3]. Previous simulations of the WW domain had shown that, in contrast with villin, it does not properly fold in MD simulations [2]. At that time it could not be determined whether the failure was due to kinetic or thermodynamic trapping. Recent free energy calculations performed to evaluate the relative stability of folded and misfolded conformations of the WW domain showed that the misfolded states are indeed thermodynamically favored over the native state. Further analysis indicated that the most likely culprit for the failure of the force field to properly rank conformations of the WW domain is the treatment of backbone hydrogen bonding, which stabilizes slightly incorrect conformations in the folded state that lead to energetic frustration and make it less favorable than a set of helical, misfolded states [4].

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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 [1] is a cellular machine that synthesizes proteins based on genetic instructions (http://www.ks.uiuc.edu/Research/ribosome). The ribosome moves along the mRNA, catches tRNAs, facilitates the pairing between codons and anti-codons, 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) [2] and X-ray crystallography [3]. 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 [3] 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.

During protein synthesis, each aminoacyl-tRNA (aa-tRNA) is delivered to the mRNA-programmed ribosome as a ternary complex with elongation factor Tu (EF-Tu) and GTP. Upon recognition of the correct tRNA, GTPase activity of EF-Tu is greatly stimulated by the ribosome and GTP hydrolysis occurs rapidly, inducing a large conformational change of EF-Tu followed by its dissociation from the ribosome and subsequent accommodation of aa-tRNA into the ribosomal A site [4]. The role of the ribosome in inducing conformational changes in EF-Tu leading to GTPase activation is not well understood. Resource scientists, jointly with the Frank laboratory, showed that GTP hydrolysis on EF-Tu is controlled by a hydrophobic gate, which opens upon interaction with the ribosome [5]. A 6.7-Angstrom resolution cryo-EM map of the aa-tRNA-EF-Tu-GDP-kirromycin ternary complex-bound E. coli ribosome was analyzed using the molecular dynamics flexible fitting (MDFF) method, recently developed by the Resource [5,6]. The analysis revealed conformational changes in the conserved switch regions of EF-Tu, including the interactions between the sarcin-ricin loop and the P-loop of EF-Tu, and between the effector loop of EF-Tu and a conserved region of the 16S rRNA. The hydrophobic gate formed by residues Val20 and Ile60 opens upon interaction with the ribosome, giving the catalytic residue His84 access to the GTP, thus triggering GTP hydrolysis. The reported work demonstrated how the ribosome induces the GTPase activity of EF-Tu via structural rearrangements of the EF-Tu switch regions.

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BTA UNIT: C

TITLE: Protecting the Cell Nucleus

KEYWORDS: nuclear pore complex, nucleoporin, FG-repeat, NTF2, nucleus, selective transport, selective barrier

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ABSTRACT: The nucleus of the eukaryotic cell is of central importance to an organism. It serves to store and organize genetic material, while separating and protecting this very important information from other cellular components. While the nucleus requires this protective isolation, it also needs to communicate with the rest of the cell, exchanging proteins and RNAs, for a variety of nuclear and cytoplasmic processes which act in concert. The nuclear pore complex (NPC) is the gatekeeper of the nucleus (http://www.ks.uiuc.edu/Research/npc/). The NPC central channel, through which all cargo is transported, is filled with unstructured proteins, commonly called FG-nups. Because of the unstructured nature of these FG-nups, however, pointed experimental study has been difficult, and as a result, the mechanism by which the NPC selectively allows transport of only certain material remains unknown. It is known, however, that in order to cross the nuclear envelope, a large molecule must first associate with a transport receptor protein (reviewed in [1–6]), which can bind to FG-nups through hydrophobic binding spots [7–13]. Understanding precisely how the FG-nups function as the selective barrier is therefore vital to determining how the NPC protects the nucleus.

In order to explore the selective barrier of an NPC, the Resource has computationally sampled a representative volume of the FG-nup-filled NPC central channel [14]. One FG-nup, namely yeast nsp1, was divided into 25 segments, each containing 100 amino acids. The resulting 25 segments were then tethered onto a planar surface, forming a 5 by 5 array. The resulting system contains more than 1 million atoms and needed to be simulated for several microseconds, which is not feasible through all-atom (AA) molecular dynamics based on current supercomputer abilities. In order to overcome this problem, a coarse-grained (CG) model [15, 16] was used to extend the simulation timescale to microseconds and AA simulations were then performed to refine the resulting CG structures. VMD [17] was used to transform the system between AA and CG representations and NAMD [18] was used to perform both the AA and CG simulations. By combining CG and AA molecular dynamics, individual nsp1 segments and arrays of them were simulated for as long as 4 microseconds. The simulations suggest a bundle-based brush-like structure for the NPC selective barrier: (i) on their surface the brush bundles are dotted with spots of amino acid pairs, phenylalanine and glycine, that are known from both simulations and experiments to interact favorably with transport receptor proteins [7–13]; (ii) the brush bundles are also interconnected, as FG-nup segments frequently switch from one bundle to another. Based on the above observations, it appears then that the FG-nups form an energetically favorable environment for transport receptor proteins and that the latter can tear FG-nup segments readily away to form a wider space for passage. To further examine the proposed mechanism through simulations, one transport receptor protein, NTF2, was then embedded into one final brush-like structure and its interaction with the brush was investigated. Although constrained by the brush bundles, multiple amino acid pairs of phenylalanine and glycine could indeed bind to the transport receptor protein NTF2 very quickly. This observation further confirms that the bundle-based brush-like structure does offer a favorable environment for transport receptor proteins. In the next year, the simulations will focus on in vitro NPC models engineered by our collaborators.

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BTA UNIT: T

TITLE: Cellular Architecture I: Membrane sculpting by BAR domains

KEYWORDS: membrane sculpting, protein-lipid interactions, multiscale, coarse grain, molecular dynamics

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ABSTRACT: Proteins from the BAR domain superfamily [1], ubiquitous in many organisms and cell types (http://www.ks.uiuc.edu/Research/BAR-domain), are implicated in a multitude of cellular processes involving membrane remodeling, e.g., endocytosis, apoptosis, and cell-cell fusion. In vitro, these proteins sculpt high-curvature membrane tubes and vesicles [2, 3] from low-curvature liposomes. BAR domains form banana-shaped homodimers bearing a high density of positively charged residues on the concave surface [4–6], which facilitates sculpting of negatively charged membranes. However, single BAR domains induce only local membrane curvature [7, 8], while recent cryo-EM reconstructions [3] reveal that sculpting of membrane tubes and vesicles is performed by many BAR domains arranged in lattice-like scaffolds.

Despite extensive studies, the dynamics of membrane sculpting by multiple BAR domains working in concert remains unresolved. It also remains unclear how BAR domain lattices are formed and maintained, and how various lattice types determine the curvature of the underlying membrane. Beyond understanding BAR domains alone, answering these questions is crucial for rendering a molecular-level picture of membrane remodeling in cells in general, since the mechanisms utilized by BAR domains are used elsewhere as well. MD simulations are well suited to study dynamics of membrane sculpting at the molecular level, but, since multiple proteins interacting simultaneously with large membrane surfaces needs to be described, all-atom MD simulations of BAR domain lattices are extremely demanding. Investigating even a small BAR domain lattice requires a simulation of a multi-million atom system over hundreds of nanoseconds, while studying membrane tubulation involves

simulation of a 100 million-atom system for hundreds of microseconds. Thus, this project poses a computational challenge, requiring massive all-atom MD simulations and coarse-grained modeling done in concert, i.e., a multiscale approach.

Resource scientists have developed models describing membrane sculpting by BAR domains at four levels of resolution [8], employing all-atom molecular dynamics, residue-based coarse graining (RBCG) that resolves single amino acids and lipid molecules, shape-based coarse graining (SBCG) that resolves overall protein and membrane shapes, and a continuum elastic membrane model. The four-scale simulations sampled many BAR domain lattice types and elucidated how the membrane curvature generated depends on the lattice type [8, 9]. Formation of entire membrane tubes by lattices of BAR domains over time scales of 200 microseconds was observed in SBCG simulations, and an all-atom simulation of a 2.3 million atom system covering 0.3 microsecond probed the dynamics of one chosen BAR domain lattice in atomic detail [9]. The lattice arrangements found to be optimal for producing high membrane curvature are composed of protein rows separated by 5 nm, the stability of the rows being maintained through electrostatic interactions between BAR domains, and bending arising due to the concerted scaffolding of the membrane by the concave surface of the proteins. Thus, a molecular mechanism for the cell-scale action of BAR domain is emerging from the computational studies [8, 9].

The BAR domain studies constitute a major driving project in the structural systems biology core of the Resource. The computational challenges inherent to the project drive the advancement of multi-million atom simulations as well as multiscale modeling. The tools developed are indispensable for modeling of other processes occurring at the sub-cellular scale, and as such contribute to the long-term effort of the Resource towards creating the framework for modeling of whole-cell at the molecular level.

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BTA UNIT: C

TITLE: Cellular Architecture II: Structural and Functional Roles of the Photosynthetic Core Complex

KEYWORDS: photosynthesis, bioenergetics, quantum biology, membrane curvature, photosynthetic unit, energy transfer, light-harvesting complex, reaction center, purple bacteria, Rhodobacter sphaeroides, flexible fitting

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ABSTRACT: The photosynthetic proteins in purple bacteria not only carry out the intricate process of energy conversion, but are also responsible for organizing the membrane into distinct cellular compartments with well-defined shapes. Indeed, electron tomography and electron microscopy have discovered that the photosynthetic proteins in purple bacteria aggregate in the membrane to form independent photosynthetic units with different shapes and sizes depending on species and protein composition. Among the membrane-bending photosynthetic proteins, the Rhodobacter sphaeroides core complex is the only one thought to induce cylindrical curvature and build tubular vesicles in bacterial cells. However, lack of high resolution structures for the core complex has rendered it difficult to investigate its membrane-bending mechanism. This project deals with a non-medical photosynthetic organism because of the principle importance of membrane morphogenesis for the cells of all organisms.

Previously, we constructed a rudimentary all-atom model for the Rhodobacter sphaeroides core complex [1] based on the then-available two-dimensional electron microscope projection map [2], and showed that the core complex, a dimeric construct, bends slightly and produces curvature in the surrounding membrane. Although these simulations explain the mechanism of core complex-induced membrane curvature, the curvature observed was insufficient to reproduce the known size of the core complex tubular vesicles due to uncertainty of the core complex structure. Recently, a three-dimensional electron miscroscope map became available, displaying a highly-bent core complex [3] and provided an opportunity to further fine-tune our understanding of the core complex structure. Combining the earlier all-atom model with the new three-dimensional density map [3] using the molecular dynamics flexible fitting method [4], an improved core complex model was generated [5, 6]. The large bending of the complex induced a high local curvature in the membrane, which agreed well with the size of the core complex tubular vesicles [5]. Furthermore, the simulations demonstrated how the local curvature properties of the RC-LH1-PufX dimer propagate to form the observed long-range organization of the Rhodobacter sphaeroides tubular vesicles [5].

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BTA UNIT: C

TITLE: Cellular Architecture III: Light Harvesting Complex II

KEYWORDS: photosynthesis, chromatophore, purple bacteria, membrane curvature, light harvesting complex

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ABSTRACT: This project deals with a problem of fundamental importance in living cells, membrane morphogenesis. The project focuses, however, on a non-medical organism, photosyntetic bacteria; their chromatophores offer a prime example of membrane morphogenisis. The chromatophores of purple photosynthetic bacteria appear to be formed by the aggregation and self-organization of the photosynthetic proteins in the membrane [1, 2]. The overall shape of the chromatophore varies among species and with protein composition and depends on the arrangement of light-harvesting complex II (LH2) and light-harvesting complex I (LH1). A combination of LH2s and dimeric LH1s results in a spherical chromatophore, as does the presence of LH2 by itself [3, 4]. Lamellar chromatophores generally contain LH2s together with monomeric LH1s [5,6]. We are interested in exploring how LH2 produces curvature, both by itself and in combination with LH1.

We found previously that hexagonally-packed LH2s in simulation equilibrate to form a curved protein patch [7]. The extent of the curvature was dependent on how closely the proteins were packed in the membrane and which bacterial species the LH2 crystal structure or model was from. All of the LH2 systems formed curvature, even those from species with naturally lamellar, i.e. flat, chromatophores, suggesting that the formation of spherical curvature via aggregation is common to all LH2s [7].

Our recent work aims to expand our understanding of the mechanism by which LH2-LH2 interactions produce curvature. It appears that each LH2 in the aggregate is inclined to tilt away from its neighbors due to a combination of steric interactions

and the electrostatic repulsion of conserved charged residues on the cytoplasmic side of the proteins. Modified LH2s in which these residues were replaced with neutral residues produced less curvature than their unmodified counterparts. We also found that LH2s packed around an LH1 monomer produced almost no curvature over the same simulation timescale of the LH2-only systems. This seems to be due in part to a mismatch in the placement of the charged residues on LH1 vs. LH2, and is consistent with the experimental observation that flat chromatophores contain mostly a homogeneous mixture of LH2s and LH1 monomers. These results have been submitted for publication. In the next year, we plan to expand our simulations to include more LH2s (as experiments suggest that higher concentrations of LH2 lead to greater curvature [4]) and to cover larger areas of mixed LH1/LH2 regions as seen in AFM images of chromatophores to better understand the interplay between the two proteins.

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BTA UNIT: C

TITLE: Multiscale Elasticity in the Muscle Protein Titin

KEYWORDS: mechanical proteins, titin, muscle, steered molecular dynamics

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DEPT2: Physics
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DEPT3: Biophysics
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INVEST4: Olga Mayans
DEGREE4: Ph.D.
DEPT4: Structural Biology
NONHOST4: University of Liverpool, UK

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ABSTRACT: Titin is a mechanical protein (http://www.ks.uiuc.edu/Research/Categories/MechBio/) that protects muscle from overstretching, which can occur following a powerful muscle contraction. Defects in the titin gene have been correlated to muscular distrophy. Titin produces a restoring force when a muscle fiber is extended beyond its normal length. Much of what is understood about titin today arose from single-molecule experiments [1–7] and computer simulations [8–13] which have shed light on how the structure of titin resist mechanical stretching forces.

The task of connecting observations in simulations to observations in experiments, however, have been limited by the cost for performing calculations that match the timescale of experiments. As a result, simulations have often focused on biological events that take place at very fast timescales that are outside the range of observation by experiments. This project has addressed this concern by improving the

performance of simulations such that they have closed the time scale gap between simulation and experiment.

Two separate studies were completed. The first study involves microsecond steered molecular dynamics (SMD) simulations of the titin I91 domain, which address the criticism that forces reported in force-probe simulations are unrealistically high compared with those measured in atomic force microscopy (AFM) experiments. The new simulations were able to accurately capture protein unfolding events as they occur in experiments, showing that MD simulations overcame the time scale limitation and produced quantitative agreement between AFM observation and simulation results. The second study, performed with Resource collaborator O. Mayans (Univ. Liverpool, UK) employed SMD and adaptive biasing force (ABF) simulations to study six connected domains of titin (I65-70). The simulations measured two different types of elasticity of titin, namely, the so-called secondary and tertiary elasticities. When simulation results were compared with experimental AFM work done on the same I65-70 region, simulations were seen to reproduce the force-extension pattern seen in experiments, but furnished a detailed atomic level view of the elastic behavior of titin.

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Resource Summary

BTA unit: (T)

NUMBER PUBLISHED -

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

NUMBER IN PRESS -

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

PUBLISHED:

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BTA unit: (C)

NUMBER PUBLISHED -

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

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

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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)

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

NUMBER IN PRESS -

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

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The Resource is currently organizing its Advisory Board meeting for September 20-21, 2009. 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 research 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, Kale, 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. Kale 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 Kale, 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, seven postdoctoral associates, 20 graduate students, three administrators, and one system administrator.

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. A 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.

Any given task carried out by the Resource is likely to involve multiple members of any one of the administrative, development, or collaborative subunits. For example a collaborative project will typically require support from development to address a software issue for a particular aspect of a project, and administrative support to organize meetings amongst collaborators. All members participate in the administration of the Resource by taking on tasks related to operation of the Resource, such as assisting in system administration tasks, or contributing to the web site. Resource members also attend regular all-member and subgroup meetings. A recently revised internal website breaks information and resources critical or useful for internal function into six main categories: administration and records, proposals and reports, computing and development, outreach and training, science and member resources, and other resources. Meeting agendas and

minutes, for example, are kept on the internal site under administration and records, providing a valuable history of group decisions and issues. And, a recent re-design of the office plan of the Resource (funded primarily by the Beckman Institute), consisting of a conference area with projection, computing/visualization stations, printing and storage cabinets, kitchenette, ad hoc meeting areas, informal seating, and large whiteboard areas, promises to facilitate internal interactions, intellection, and collaborations with the scientific community.

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:

- 21,876 additional downloaders of VMD
- 5,609 additional downloaders 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/`

- 905 additional registered users of BioCoRE
- 4,904 VMD emails, 305 NAMD emails, and more than 800 BioCoRE chats and emails were exchanged in user support
- 3,340 citations of the VMD source paper; 1,351 citations of the NAMD source papers
- over 320,000 unique visitors to Resource software web site
- 12 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 been downloaded by 130,713 users as of April 2009 (an increase of 21,878 or +20% since March 2008), with 28,178 of those 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 53,375 downloading users since its release in April 2007, with 9,910 or 19% of downloaders indicating they are NIH funded users.

NAMD has been downloaded by 30,806 users (as of April 2009) (an increase of 5,609 or +22% since March 2008), of whom 6,005 or 19% are repeat downloaders. 5,299 (17%) of NAMD downloaders are NIH funded. The current version of NAMD, version 2.6 released in August 2006, has 15,400 downloading users, with 2,802 or (18%) of downloaders indicating NIH funding. The new NAMD beta, version 2.7b1, has 1600 downloading users in the two months since it's release in March.

BioCoRE has 3,651 registered users (an increase of 905, or +33% in the past year), involved in 550 projects (compared to 516 a year ago). A total of 207 projects within BioCoRE have been reported as either fully or partially NIH-funded.

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

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.

VMD Enhancements for 2008-2009 include amongst other features:

- The VMD plugin interface, the psfgen plugin, the solvate plugin, and the VMD internal data structures have been extensively revised to enable support for extremly large structures containing over one hundred million atoms. Models containing over 116 million atoms have been successfully constructed using the new version of VMD.
- VMD now makes extensive use of GPU-accelerated algorithms to achieve high performance for computationally demanding tasks, such as calculation of electrostatic fields surrounding molecular structures, calculation of molecular orbital grids, and acceleration of the implicit ligand sampling method.
- VMD now supports improved analysis for the display of carbohydrate structures, implementing an improved version of recently described techniques [1]
- VMD along with Tachyon now provides built-in support for sophisticated ambient occlusion lighting, for use in publication renderings and movie making.
- 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 8.5.6 of the Tcl scripting language, providing greater flexibility for user script development

Scope of VMD User Support:

- 4,904 e-mail exchanges in response to user inquiries sent to the vmd@ks.uiuc.edu e-mail address
- 843 subscribers to the VMD-L mailing list, with 13,764 total postings, and 2,053 postings for the May 2008 - April 2009 period
- Local face-to-face support has been provided

There are currently 550 non-Resource users with access to the VMD source code repository, with 92 such users added in the last year.

Sites with Links to the VMD Site (via Yahoo! site search, April 2009): 4,001 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 petaflop parallel computers.

NAMD Enhancements for 2008-2009 include among other features:

- Collective variable-based calculations
- Improved free energy methods for alchemical transformations
- Grid-based forces and molecular dynamics flexible fitting
- Additional bonded terms for restraining molecular structure
- Plugin-based support for binary molecular data structure formats
- Support for loading systems of 100-million atoms
- Improved parallelization on GPU-accelerated clusters
- Specialized implementation of particle-mesh Ewald for Blue Gene
- Ports to NCSA Lincoln cluster and NICS Kraken XT5

NAMD Availability in Supercomputer Centers:

- Pittsburgh Supercomputing Center
- National Center for Supercomputing Applications
- Indiana University
- Texas Advanced Computing Center
- National Institute for Computational Sciences
- Oak Ridge National Laboratory
- Argonne National Laboratory

Scope of NAMD User Support:

- The NamdWiki user-editable web site contains 52 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"
- 723 subscribers to the NAMD-L mailing list, with 9,919 total postings, and 2,302 postings for the May 2008 - April 2009 period
- Over 305 emails exchanged with users via the namd@ks.uiuc.edu e-mail address, a number which excludes questions sent to the Charm++ developers, directly to individual NAMD developers, or to the NAMD and VMD mailing lists.
- Local face-to-face support has been provided

There are currently 488 users with access to the NAMD source code repository, with 161 users added in the last year.

A new automated nightly build system makes the latest NAMD source code and Linux x86_64 binaries available for immediate download by users without repository access. These nightly builds were downloaded 683 times by 389 users in the two months since their introduction in March.

Sites with Links to NAMD site (via Yahoo! site search, April 2009): 1,728 links

BioCoRE User Support:

- 30 emails issued to/from biocore@ks.uiuc.edu from April 2008 - March 2009
- more than 800 chat messages sent to the BioCoRE public help project from April 2008 - March 2009 within BioCoRE itself.

Sites with Links to BioCoRE site (via Yahoo! site search, April 2009): 408 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 2009 yielded 3,340 published journal articles, papers, or books citing the VMD origin paper [2]. Below are 25 recent citations:

- Shi, R., Proteau, A., Wagner, J., Cui, Q. Z., Purisima, E. O., Matte, A., et al. (2009). Trapping open and closed forms of FitE-A group III periplasmic binding protein. *Proteins-Structure Function and Bioinformatics*, 75(3), 598-609.

- Peters, G. H. (2009). The effect of Asp54 phosphorylation on the energetics and dynamics in the response regulator protein SpoOF studied by molecular dynamics. *Proteins-Structure Function and Bioinformatics*, 75(3), 648-658.

- Liu, T., Chen, F. J., Tang, N., Feng, J. M., Zhao, D. S., Wei, K. H., et al. (2009). CD247 can bind SHC1, no matter if CD247 is phosphorylated. *Journal of Molecular Recognition*, 22(3), 205-214.

- Taranta, M., Bizzarri, A. R., & Cannistraro, S. (2009). Modelling the interaction between the N-terminal domain of the tumor suppressor p53 and azurin. *Journal of Molecular Recognition*, 22(3), 215-222.

- Bhowmik, R., Katti, K. S., & Katti, D. R. (2009). Mechanisms of Load-Deformation Behavior of Molecular Collagen in Hydroxyapatite-Tropocollagen Molecular System: Steered Molecular Dynamics Study. *Journal of Engineering Mechanics-Asce*, 135(5), 413-421.

- Carvajal-Diaz, J. A., Liu, L. J., & Cagin, T. (2009). Structure and Dynamics of Water Within Single Wall Carbon Nanotubes and Self-Assembled Cyclic Peptide Nanotubes. *Journal of Computational and Theoretical Nanoscience*, 6(4), 894-902.

- Maier, E. M., Gersting, S. W., Kemter, K. F., Jank, J. M., Reindl, M., Messing, D. D., et al. (2009). Protein misfolding is the molecular mechanism underlying MCADD identified in newborn screening. *Human Molecular Genetics*, 18(9), 1612-1623.

- Imbrici, P., Grottesi, A., D'Adamo, M. C., Mannucci, R., Tucker, S. J., & Pessia, M. (2009). Contribution of the central hydrophobic residue in the PXP motif of voltage-dependent K+ channels to S6 flexibility and gating properties. *Channels*, 3(1), 39-45.

- Demir, O., & Roitberg, A. E. (2009). Modulation of Catalytic Function by Differential Plasticity of the Active Site: Case Study of Trypanosoma cruzi trans-Sialidase and Trypanosoma rangeli Sialidase. *Biochemistry*, 48(15), 3398-3406.

- Matsumoto, F., Maeda, K., Chatake, T., Maeda, Y., & Fujiwara, S. (2009). Functional aberration of myofibrils by cardiomyopathy-causing mutations in the coiled-coil region of the troponin-core domain. *Biochemical and Biophysical Research Communications*, 382(1), 205-209.

- Mothana, B., Roy, S., & Rauk, A. (2009). Molecular dynamics study of the interaction of A beta(13-23) with beta-sheet inhibitors. *Arkivoc*, 116-134.
- Zhang, L. Q., Van Orman, J. A., & Lacks, D. J. (2009). Effective radii of noble gas atoms in silicates from first-principles molecular simulation. *American Mineralogist*, 94(4), 600-608.
- Shen, X. Y., Lu, Y., & Li, S. M. (2009). Molecular Dynamics Simulations on the Stability of (3+1) Mixed-Type Hybrid G-quadruplex in Human Telomere. *Acta Physico-Chimica Sinica*, 25(4), 783-791.
- Liu, B., Li, X. Y., Li, B. L., Xu, B. Q., & Zhao, Y. L. (2009). Carbon Nanotube Based Artificial Water Channel Protein: Membrane Perturbation and Water Transportation. *Nano Letters*, 9(4), 1386-1394.
- Warren, D. B., Chalmers, D. K., & Pouton, C. W. (2009). Structure and Dynamics of Glyceride Lipid Formulations, with Propylene Glycol and Water. *Molecular Pharmaceutics*, 6(2), 604-614.
- Jetton, N., Rothberg, K. G., Hubbard, J. G., Wise, J., Li, Y., Ball, H. L., et al. (2009). The cell cycle as a therapeutic target against Trypanosoma brucei: Hesperadin inhibits Aurora kinase-1 and blocks mitotic progression in bloodstream forms. *Molecular Microbiology*, 72(2), 442-458.
- Roberts, B. P., Scanlon, M. J., Krippner, G. Y., & Chalmers, D. K. (2009). Molecular Dynamics of Poly(L-lysine) Dendrimers with Naphthalene Disulfonate Caps. *Macromolecules*, 42(7), 2775-2783.
- Roberts, B. P., Krippner, G. Y., Scanlon, M. J., & Chalmers, D. K. (2009). Molecular Dynamics of Variegated Polyamide Dendrimers. *Macromolecules*, 42(7), 2784-2794.
- Lange, A. W., & Herbert, J. M. (2009). Both Intra- and Interstrand Charge-Transfer Excited States in Aqueous B-DNA Are Present at Energies Comparable To, or Just Above, the (1)pi pi* Excitonic Bright States. *Journal of the American Chemical Society*, 131(11), 3913-3922.
- Morton, S. M., & Jensen, L. (2009). Understanding the Molecule-Surface Chemical Coupling in SERS. *Journal of the American Chemical Society*, 131(11), 4090-4098.
- Ganguly, D., & Chen, J. H. (2009). Atomistic Details of the Disordered States of KID and pKID. Implications in Coupled Binding and Folding. *Journal of the American Chemical Society*, 131(14), 5214-5223.

- Raju, S. G., & Balasubramanian, S. (2009). Aqueous Solution of bmim PF6 : Ion and Solvent Effects on Structure and Dynamics. *Journal of Physical Chemistry B*, 113(14), 4799-4806.

- Yang, Y., & Cui, Q. (2009). Does Water Relay Play an Important Role in Phosphoryl Transfer Reactions? Insights from Theoretical Study of a Model Reaction in Water and tert-Butanol. *Journal of Physical Chemistry B*, 113(14), 4930-4939.

- Karayiannis, N. C., Laso, M., & Kroger, M. (2009). Detailed Atomistic Molecular Dynamics Simulations of alpha-Conotoxin AuIB in Water. *Journal of Physical Chemistry B*, 113(15), 5016-5024.

- Khandelia, H., Jensen, M. O., & Mouritsen, O. G. (2009). To Gate or Not To Gate: Using Molecular Dynamics Simulations To Morph Gated Plant Aquaporins into Constitutively Open Conformations. *Journal of Physical Chemistry B*, 113(15), 5239-5244.

List of papers citing NAMD: A literature search in the ISI Web of Science citation database in April 2009 yielded 1,351 published journal articles, papers, or books citing the current [3] or prior [4] NAMD origin papers. Below are 25 recent cites:

- Olsson, J. D. M., Landstrom, J., Ronnols, J., Oscarson, S., & Widmalm, G. (2009). Synthesis of and molecular dynamics simulations on a tetrasaccharide corresponding to the repeating unit of the capsular polysaccharide from Salmonella enteritidis. *Organic & Biomolecular Chemistry*, 7(8), 1612-1618.

- Suter, J. L., Anderson, R. L., Greenwell, H. C., & Coveney, P. V. (2009). Recent advances in large-scale atomistic and coarse-grained molecular dynamics simulation of clay minerals. *Journal of Materials Chemistry*, 19(17), 2482-2493.

- Wan, S. Z., & Coveney, P. V. (2009). A Comparative Study of the COX-1 and COX-2 Isozymes Bound to Lipid Membranes. *Journal of Computational Chemistry*, 30(7), 1038-1050.

- Carvajal-Diaz, J. A., Liu, L. J., & Cagin, T. (2009). Structure and Dynamics of Water Within Single Wall Carbon Nanotubes and Self-Assembled Cyclic Peptide Nanotubes. *Journal of Computational and Theoretical Nanoscience*, 6(4), 894-902.

- Matsumoto, F., Maeda, K., Chatake, T., Maeda, Y., & Fujiwara, S. (2009). Functional aberration of myofibrils by cardiomyopathy-causing mutations in the coiled-coil region of the troponin-core domain. *Biochemical and Biophysical Research Communications*, 382(1), 205-209.

- Quick, M., Winther, A. M. L., Shi, L., Nissen, P., Weinstein, H., & Javitch, J. A. (2009). Binding of an octylglucoside detergent molecule in the second substrate (S2) site of LeuT establishes an inhibitor-bound conformation. *Proceedings of the National Academy of Sciences of the United States of America*, 106(14), 5563-5568.

- Liu, B., Li, X. Y., Li, B. L., Xu, B. Q., & Zhao, Y. L. (2009). Carbon Nanotube Based Artificial Water Channel Protein: Membrane Perturbation and Water Transportation. *Nano Letters*, 9(4), 1386-1394.

- Kang, Y. K., Lee, O. S., Deria, P., Kim, S. H., Park, T. H., Bonnell, D. A., et al. (2009). Helical Wrapping of Single-Walled Carbon Nanotubes by Water Soluble Poly(p-phenyleneethynylene). *Nano Letters*, 9(4), 1414-1418.

- Jetton, N., Rothberg, K. G., Hubbard, J. G., Wise, J., Li, Y., Ball, H. L., et al. (2009). The cell cycle as a therapeutic target against Trypanosoma brucei: Hesperadin inhibits Aurora kinase-1 and blocks mitotic progression in bloodstream forms. *Molecular Microbiology*, 72(2), 442-458.

- Roberts, B. P., Scanlon, M. J., Krippner, G. Y., & Chalmers, D. K. (2009). Molecular Dynamics of Poly(L-lysine) Dendrimers with Naphthalene Disulfonate Caps. *Macromolecules*, 42(7), 2775-2783.

- Roberts, B. P., Krippner, G. Y., Scanlon, M. J., & Chalmers, D. K. (2009). Molecular Dynamics of Variegated Polyamide Dendrimers. *Macromolecules*, 42(7), 2784-2794.

- Swift, R. V., & McCammon, J. A. (2009). Substrate Induced Population Shifts and Stochastic Gating in the PBCV-1 mRNA Capping Enzyme. *Journal of the American Chemical Society*, 131(14), 5126-5133.

- Masetti, M., Cavalli, A., Recanatini, M., & Gervasio, F. L. (2009). Exploring Complex Protein-Ligand Recognition Mechanisms with Coarse Metadynamics. *Journal of Physical Chemistry B*, 113(14), 4807-4816.

- Khandelia, H., Jensen, M. O., & Mouritsen, O. G. (2009). To Gate or Not To Gate: Using Molecular Dynamics Simulations To Morph Gated Plant Aquaporins into Constitutively Open Conformations. *Journal of Physical Chemistry B*, 113(15), 5239-5244.

- Xu, D., Newhouse, E. I., Amaro, R. E., Pao, H. C., Cheng, L. S., Markwick, P. R. L., et al. (2009). Distinct Glycan Topology for Avian and Human Sialopentasaccharide Receptor Analogues upon Binding Different Hemagglutinins: A Molecular Dynamics Perspective. *Journal of Molecular Biology*, 387(2), 465-491.

- Nyblom, M., Frick, A., Wang, Y., Ekvall, M., Hallgren, K., Hedfalk, K., et al. (2009). Structural and Functional Analysis of SoPIP2;1 Mutants Adds Insight into Plant Aquaporin Gating. *Journal of Molecular Biology*, 387(3), 653-668.

- Tatsis, V. A., Tsoulos, I. G., & Stavrakoudis, A. (2009). Molecular Dynamics Simulations of the TSSPSAD Peptide Antigen in Free and Bound with CAMPATH-1H Fab Antibody States: The Importance of the beta-Turn Conformation. *International Journal of Peptide Research and Therapeutics*, 15(1), 1-9.

- Lee, T. S., Ma, W. L., Zhang, X., Giles, F., Kantarjian, H., & Albitar, M. (2009). Mechanisms of Constitutive Activation of Janus Kinase 2-V617F Revealed at the Atomic Level Through Molecular Dynamics Simulations. *Cancer*, 115(8), 1692-1700.

- Kang, Y., Liu, Y. C., Wang, Q., Shen, J. W., Wu, T., & Guan, W. J. (2009). On the spontaneous encapsulation of proteins in carbon nanotubes. *Biomaterials*, 30(14), 2807-2815.

- Hardy, D. J., Stone, J. E., & Schulten, K. (2009). Multilevel summation of electrostatic potentials using graphics processing units. *Parallel Computing*, 35(3), 164-177.

- Gajdanowicz, P., Garcia-Mata, C., Gonzalez, W., Morales-Navarro, S. E., Sharma, T., Gonzalez-Nilo, F. D., et al. (2009). Distinct roles of the last transmembrane domain in controlling Arabidopsis K+ channel activity. *New Phytologist*, 182(2), 380-391.

- Gallo, M. T., Grant, B. J., Teodoro, M. L., Melton, J., Cieplak, P., Phillips, G. N., et al. (2009). Novel procedure for thermal equilibration in molecular dynamics simulation. *Molecular Simulation*, 35(5), 349-357.

- Matsunaga, Y., Fuchigami, S., & Kidera, A. (2009). Multivariate frequency domain analysis of protein dynamics. *Journal of Chemical Physics*, 130(12).

- Zanuy, D., Curco, D., Nussinov, R., & Aleman, C. (2009). Influence of the Dye Presence on the Conformational Preferences of CREKA, a Tumor Homing Linear Pentapeptide. *Biopolymers*, 92(2), 83-93.

- Cheng, Y., Pei, Q. X., & Gao, H. J. (2009). Molecular-dynamics studies of competitive replacement in peptide-nanotube assembly for control of drug release. *Nanotechnology*, 20(14).

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 [5]:

- 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., Wronski, M., Nowinski, A., Nowinski, 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., Pytlinski, 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.

- Pytlinski, J., Skorwider, L., Benedyczak, K., Wronski, 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 2008 - March 2009) 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	228,667	24,414
NAMD	130,902	10,908
BioCoRE	22,534	1,879

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.

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

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

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

- *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 2008 to March 2009, the Resource has hosted 11 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 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.

Seminars 2008-2009

Between May 2008 and April 2009 the Resource organized and hosted 12 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 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:

- Apr 20, 2009, Dr. Michael F. Brown, University of Arizona, Tucson, Arizona, *Dynamics of Rhodopsin as Illuminated by Solid-State NMR*

- Mar 30, 2009, Dr. Ioan Kosztin, University of Missouri, Columbia, MO, *Anomalous Diffusion of Lipid Atoms and Molecules in Phospholipid Bilayers: a Combined Molecular Dynamics and Theoretical Study*

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

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

- Mar 5, 2009, Dr. Trevor Sewell, University of Cape Town, Rondebosch, South Africa, *Towards Atomic Insights from Macromolecular Electron Microscopic Reconstructions*

- Feb 23, 2009, Dr. David Cerutti, Vanderbilt University, Nashville, TN, *Enhanced Validation and Execution of Biomolecular Simulations: From Lattice Simulations to Lattice Sums"*

- Dec 8, 2008, Professor Jamie Cate, University of California, Berkeley, Berkeley, CA, *Antibiotic Inhibition of the Universal Translator, the Ribosome*

- Nov 24, 2008, Dr. Franois Dehez , Nancy Universit , Cedex, France, *Intermolecular Potentials: Ensuring A Physical Description Of Both Polarizability And Polarization*

- Nov 3, 2008, Professor Govindjee, University of Illinois at Urbana-Champaign, Urbana, Illinois, *Rebirth of Photosynthesis Research*

- Oct 6, 2008, Dr. Jon Erickson, Lilly Research Laboratories, Indianapolis, IN, *Challenges of Ligand Binding Mode Prediction for use in Drug Design*

- Sep 24, 2008, Dr. Christophe Chipot, Nancy Universit, CNRS, Vandoeuvre-les-Nancy, France, *Binding of ADP in the Mitochondrial ADP/ATP Carrier is driven by an Electrostatic Funnel*

- Sep 15, 2008, Dr. Ilia Solov'yov, Frankfurt Institute of Advanced Studies and Physics Department, University of Frankfurt, Frankfurt, Germany, *Magnetic Clusters in the Beak of a Bird: A Mechanism of Magnetoreception*

- Jul 25, 2008, Professor Modesto Orozco, University of Barcelona, Barcelona, Spain, *The World of DNA: From Quantum Mechanics to Genomics*

- Jul 7, 2008, Professor Markus Meuwly, University of Basel, Basel, Switzerland, *Quantitative Atomistic Simulations: Dynamics and Spectroscopy of Heterogeneous Systems in Biology and Physics*

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:

- 41 published articles and 10 in press in refereed journals or other publications
- Over 830,000 unique visitors to the Resource web site
- Over 24,000 article downloads from the Resource's publications database
- 1,230 reprint requests fulfilled by Resource staff
- 57 talks by Resource faculty and 30 presentations by other members
- 43 news stories about the Resource in various media outlets
- 66 requests to use Resource images or movies from external publishers or presenters
- Over 21,700 new 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 10 articles currently in press and 41 published articles by Resource members and collaborators published over the last year.

Articles In Press

- Eduardo R. Cruz-Chu, Thorsten Ritz, Zuzanna S. Siwy, and Klaus Schulten. Molecular control of ionic conduction in polymer nanopores. *Faraday Discussion*, 143, 2009. In press.
- J. Dittmer, L. Thøgersen, J. Underhaug, K. Bertelsen, Th. Vosegaard, J. M. Pedersen, B. Schiøtt, E. Tajkhorshid, T. Skrydstrup, and N. Chr. Nielsen. Incorporation of Antimicrobial Peptides into Membranes: A Combined Liquid-State NMR and Molecular Dynamics Study of Alamethicin in DMPC/DHPC Bicelles. *Journal of Physical Chemistry B*, 2009, In press.

- B. Dorvel, G. Sigalov, Q. Zhao, V. Dimitrov, U. Mirsaidov, A. Aksimentiev and G. Timp. Analyzing the forces binding restriction endonucleases to DNA using a synthetic nanopore. *Nucleic Acid Research*, 2009. In press.

- Jen Hsin, James Gumbart, Leonardo G. Trabuco, Elizabeth Villa, Pu Qian, C. Neil Hunter, and Klaus Schulten. Protein-induced membrane curvature investigated through molecular dynamics flexible fitting. *Biophysical Journal*, 2009. In press.

- C. Maffeo and A. Aksimentiev. Structure, dynamics, and ion conductance of a phospho-lamban pentamer. *Biophysical Journal*, 2009. In press.

- James C. Phillips, John E. Stone, and Klaus Schulten. Adapting a message-driven parallel application to GPU-accelerated clusters. In *SC '08: Proceedings of the 2008 ACM/IEEE Conference on Supercomputing*, pp. 1-9, Piscataway, NJ, USA, 2008. IEEE Press.

- E. Roberts, J. Stone, L. Sepulveda, Wen-mei Hwu, and Z. Luthey-Schulten. Long time-scale simulations of in vivo diffusion using GPU hardware. *Proceedings 8th IEEE International Meeting on High Performance Computational Biology*, 2009. In press.

- Ilia A. Solov'yov and Klaus Schulten. Magnetoreception through cryptochrome may involve superoxide. *Biophysical Journal*, 2009. In press.

- Leonardo G. Trabuco, Elizabeth Villa, Eduard Schreiner, Christopher B. Harrison, and Klaus Schulten. Molecular dynamics flexible fitting: A practical guide to combine cryo-electron microscopy and x-ray crystallography. *Methods*, 2009. In press.

- Ying Yin, Anton Arkhipov, and Klaus Schulten. Simulations of membrane tubulation by lattices of amphiphysin N-BAR domains. *Structure*, 2009. In press.

Published Articles

- Peter L. Freddolino, Sanghyun Park, Benoit Roux, and Klaus Schulten. Force field bias in protein folding simulations. *Biophysical Journal*, 96:3772-3780, 2009.

- Aleksei Aksimentiev, Robert K. Brunner, Eduardo Cruz-Chu, Jeffrey Comer, and Klaus Schulten. Modeling transport through synthetic nanopores. *IEEE Nanotechnology*, 3:20-28, 2009.

- Anton Arkhipov and Klaus Schulten. Limits for reduction of effective focal volume in multiple-beam light microscopy. *Optics Express*, 17:2861-2870, 2009.

- Anton Arkhipov, Ying Yin, and Klaus Schulten. Four-scale description of membrane sculpting by BAR domains. *Biophysical Journal*, 95:2806-2821, 2008.

- R. Carr, I. A. Weinstock, A. Sivaprasadarao, A. Müller and A. Aksimentiev. Self-assembly route for embedding polyoxomolybdate capsules in lipid bilayer membranes. *Nano Letters*, 8:39163921, 2008.

- 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.

- Danielle Chandler, Jen Hsin, Christopher B. Harrison, James Gumbart, and Klaus Schulten. Intrinsic curvature properties of photosynthetic proteins in chromatophores. *Biophysical Journal*, 95:2822-2836, 2008.

- V. Cherezonv, W. Liu, J. Derrick, B. Luan, A. Aksimentiev, V. Katruc, and M. Carey. In meso crystal structure and computer simulations suggest an alternative proteoglycan binding site in the OpcA outer membrane adhesin. *Protein: Structure, Function, and Bioinformatics*, 71:24-34, 2008.

- J. Comer, V. Dimitrov, G. Timp, and A. Aksimentiev. Microscopic mechanics of hairpin DNA tranlocation through synthetic nanopores. *Biophysical Journal*, 96: 593608, 2009.

- J. Eargle, A. A. Black, A. Sethi, L. G. Trabuco, Z. Luthey-Schulten. Dynamics of Recognition between tRNA and elongation factor Tu. *Journal of Molecular Biology* 377:1382-405, 2008.

- Eduardo R. Cruz-Chu, Aleksei Aksimentiev, and Klaus Schulten. Ionic current rectification through silica nanopores. *Journal of Physical Chemistry C*, 113:1850-1862, 2009.

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The Resource actively supports the NIH Public Access law and ensures compliance for all of its NIH-funded publications.

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 830,000 unique visitors to the Resource web site, an average of 69,000 per month during the April 2008 – March 2009 period; visits during that period resulted in 2.3 terabytes 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, 2009) found that 15,121 external sites link into areas of the Resource web site, with 1,107 sites linking directly to the home page.

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

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

	Total Visitors	Visitors per Month
VMD	228,667	19,055
NAMD	130,902	10,908
BioCoRE	22,554	1,897
Other Research	168,888	14,074
Galleries	36,084	3,007
Publications	39,593	3,299
Seminars	5,569	464

Table 2: Web site visitors from April 2008 - March 2009

by title, author(s), journal, subject, year ranges, and fulltext searching. Over 24,000 unique visitors downloaded at least one file copy of an article using the database over the April 2008 – March 2009 period. Additionally, 1,230 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

- April 2009, New Haven, CT, Yale University, Departments of Mechanical Engineering and Physics, "The Computational Microscope"
- March 2009, Bad Staffelstein, Germany, Light Harvesting Processes 2009, "Form-follows-Function Architecture of Purple Bacterial Light Harvesting Systems"
- March 2009, Munich, Germany, Workshop on Molecular Modelling on Supercomputers, "Structural Systems Biology"
- March 2009, Juelich, Germany, Juelich Winter School 2009, Multiscale Simulation Methods in Molecular Sciences, "Application of Residue-Based Coarse Graining to Biomolecular Simulations"
- February 2009, Chicago, IL, AAAS Annual Meeting, "The Computational Microscope"

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

- February 2009, Stanford, CA, Stanford University, OpenMM Workshop and Molecular Dynamics Symposium, "Biomolecular Modeling with VMD and NAMD Accelerated Through Graphics Processing Units"
- January 2009, Urbana, IL, University of Illinois at Urbana-Champaign, Micro and Nanotechnology Laboratory (MNTL), Seminar Series of the Center for Cellular Mechanics, "Discovery Through the Computational Microscope"
- January 2009, Chicago, IL, Loyola University, Chemistry Seminar Series, "The Chemical Compass of Animal Magnetotaxis"
- December 2008, Rockville, MD, University of Maryland Biotechnology Institute, CARB's (Center for Advanced Research in Biotechnology) External Speaker Series, "Cellular Systems and Processes Viewed through Hybrid Methods of Observation and Modeling"
- December 2008, Houston, TX, University of Houston, NCMI Workshop on Single Particle Reconstruction, "Cellular Systems and Processes viewed through Hybrid Methods of Observation and Modeling"
- April 2009, New Haven, CT, Yale University, Departments of Mechanical Engineering and Physics, "The Computational Microscope"
- March 2009, Bad Staffelstein, Germany, Light Harvesting Processes 2009, "Form-follows-Function Architecture of Purple Bacterial Light Harvesting Systems"
- March 2009, Munich, Germany, Workshop on Molecular Modelling on Supercomputers, "Structural Systems Biology"
- March 2009, Juelich, Germany, Juelich Winter School 2009, Multiscale Simulation Methods in Molecular Sciences, "Application of Residue-Based Coarse Graining to Biomolecular Simulations"
- February 2009, Chicago, IL, AAAS Annual Meeting, "The Computational Microscope"
- February 2009, Stanford, CA, Stanford University, OpenMM Workshop and Molecular Dynamics Symposium, "Biomolecular Modeling with VMD and NAMD Accelerated Through Graphics Processing Units"
- January 2009, Urbana, IL, University of Illinois at Urbana-Champaign, Micro and Nanotechnology Laboratory (MNTL), Seminar Series of the Center for Cellular Mechanics, "Discovery Through the Computational Microscope"

- January 2009, Chicago, IL, Loyola University, Chemistry Seminar Series, "The Chemical Compass of Animal Magnetotaxis"
- December 2008, Urbana, IL, 161 Noyes, UIUC Chapter, National Organization for the Professional Advancement of Black Chemists and Chemical Engineers (NOBCChE), "Making Discoveries in Biology with the Computational Microscope"
- November 2008, Urbana, IL, Dial Club, "The Animal Compass"
- November 2008, Urbana, IL, University of Illinois at Urbana-Champaign, Physics of Living Cells, Physics Frontier Center, "Physical Mechanism of Protein Elongation In The Ribosome"
- October 2008, Atlanta, GA, Georgia Tech, International Launch Conference, Frontiers in Multi-Scale Systems Biology, "Cellular Systems and Processes viewed through Hybrid Methods of Observation and Modeling"
- September 2008, Urbana, IL, University of Illinois at Urbana-Champaign, Siebel Center, UIUC SIAM Student Chapter Colloquia, "Advanced Computing in Biology and Bioengineering"
- September 2008, Tucson, AZ, University of Arizona, Erying Lectures in Chemistry and Biochemistry, "Physics of Photosynthesis in Purple Bacteria"
- September 2008, Tempe, AZ, Arizona State University, Erying Lectures in Chemistry and Biochemistry, "Computational Microscopy of the Living Cell"
- September 2008, Lansing, MI, Michigan State University, Quantitative Biology & Modeling Science at the Edge series, "Molecular Dynamics Simulations Beyond Microsecond, Beyond Million Atoms, Beyond Present Force Fields"
- August 2008, Santa Fe, NM, Workshop on Nuclear Pore Complex: Biology, Physics and Nanotechnology, "Gating Mechanism of the Nuclear Pore Complex Studied Through Molecular Dynamics"
- July 2008, Saxtons River, VT, FASEB, Molecular Biophysics of Cellular Membranes, "Computational Modeling of Proteins Sensing and Controlling Cellular Membrane Mechanics"
- June 2008, Ascona, Switzerland, 2008 President's Meeting of the International Society of Quantum Biology and Pharmacology (ISQBP), "Molecular Dynamics Simulations Beyond Microsecond, Beyond Million Atoms, Beyond Present Force Fields"
- June 2008, Sitges, Spain, XXI Sitges Conference on Statistical Mechanics, "Coarse Graining in Biomolecular Simulations"

- June 2008, Barcelona, Spain, Barcelona Supercomputing Center, Grand Challenges in Computational Biology, "The Computational Microscope"

Laxmikant Kale

- August 2008, Urbana, IL, University of Illinois at Urbana-Champaign, Universal Parallel Computing Research Center, "Simplifying Parallel Programming with Incomplete Parallel Languages"
- July 2008, Seattle, WA, Scientific Discovery through Advanced Computing (SciDAC) 2008, "Some Essential Techniques for Developing Efficient Petascale Applications"

Zan Luthey-Schulten

- December 2008, Bowling Green, OH, Bowling Green State University, "On the Evolution of Translation: Dynamics of Recognition in Protein/RNA Complexes"
- November 2008, Urbana, IL, University of Illinois at Urbana-Champaign, Physics Frontier Center symposium, "Towards Lattice Simulations of in vivo Translation"
- October 2008, Indianapolis, IN, Indiana University School of Medicine, Center for Computational Biology and Bioinformatics, "On the Evolution of Translation
- September 2008, Phoenix, AZ, Arizona State University, Department of Chemistry Biochemistry, "Dynamics of Recognition and Signaling in Protein/RNA Complexes"
- September 2008, Annecy, France, AARS Meeting, "Migration tRNA from GluRs to EF-Tu"
- August 2008, Philadelphia, PA, ACS Meeting, Computional Chemistry Session, "Dynamics of Recognition in Protein/RNA Complexes:Evolution of Translation"
- June 2008, Munich, Germany, Technical University Munich, Chemistry Department, "Dynamics of Recognition in Protein/RNA Complexes"
- June 2008, Munich, Germany, Ludwig Maximillian University Munich, Applied Physics Institute, "Dynamics of Recognition in Protein/RNA Complexes: Evolution of Translation"

Emad Tajkhorshid

- February 2009, Saint Simons, GA, 49th Sanibel Symposium, "Dynamics of Active Transport Across Cellular Membranes at Full Atomic Resolution"
- January 2009, New Haven, CT, Yale University, Department of Physiology, "Dynamics of Active Transport Across Cellular Membranes at Full Atomic Resolution"
- October 2008, Chicago, IL, University of Illinois at Chicago, Department of Pharmacology, "An Atomic-Resolution View of Membrane Binding and Activation of Blood Coagulation Factors"
- October 2008, Newark, DE, University of Delaware, Delaware Membrane Protein Symposium, "Dynamics of Active Transport Across Cellular Membranes at Full Atomic Resolution"
- September 2008, New York, NY, New York University, "Visualizing the Art of Active Transport Across Cellular Membranes at Sub-Angstrom Resolution"
- July 2008, Telluride, CO, Telluride Science Research Center, Protein Electrostatic Workshop, "A Dynamical View of Membrane Transporters - Electrostatic Aspect of Transport"
- May 2008, Calgery, Alberta, Canada, University of Calgary, "Visualizing the Art of Active Transport Across Cellular Membranes at Full Atomic Resolution"
- May 2008, Ashburn, VA, HHMI Janelia Farm Research Campus, Conference on Force-Gated Ion Channels: From Structure to Sensation, "Ion Binding and Channel Opening of Acid Sensing Ion Channel-1"

Alek Aksimentiev

- October 2008, Yokohoma, Japan, Yokohama City University, Department of Supramolecular Biology, "Molecular Dynamics Simulations of DNA Micromechanics"
- September 2008, Urbana, IL, University of Illinois at Urbana-Champaign, NSF Center for Advanced Materials for Water Purification, "Nanomachines: State of the Art, Perspectives and Challenges"
- September 2008, Liege, Belgium, Fourth Focused Workshop on Electronic Recognition of Biomolecules, "Effective Force, Electro-Osmotic Flow and Charge Inversion in a Solid-State Nanopore"
- July 2008, Yorktown Heights, NY, IBM T. J. Watson Research Center, "Modeling Silicon Nanopores for Sequencing DNA"

- May 2008, Grenoble, France, INRIA, SeMoVi Seminar, "Modeling Silicon Nanopores for Detection and Manipulation of Single Biomolecule"

- April 2008, Urbana, IL, University of Illinois at Urbana-Champaign, Department of Mechanical Engineering, "Micromechanics of DNA"

Other TCB members (includes meetings attended and poster sessions)

- April 2009, Urbana, IL, Beckman Institute for Advanced Science and Technology, Graduate Student Seminar Series, "Molecular Dynamics Simulations of Villin Headpiece Folding" (Peter Freddolino), "Membrane Sculpting by BAR Domain Proteins" (Ying Yin)

- April 2009, Urbana, IL, National Center for Supercomputing Applications, Path to Petascale: Adapting GEO/CHEM/ASTRO Applications for Accelerators and Accelerator Clusters, "Experience with NAMD on GPU-accelerated Clusters" (Jim Phillips)

- March 2009, Salt Lake City, UT, Spring 2009 American Chemical Society Meeting, "Biomolecular Applications of Graphics Processors: High Performance Computation and Interactive Display of Molecular Orbitals" (Jan Saam)

- March 2009, Urbana, IL, Beckman Institute for Advanced Science and Technology, Beckman Institute Open House 2009, "A Journey Through Molecules of Life with Your Friendly Neighborhood Biophysicist" (Melih Sener)

- February-March 2009, Boston, MA, Biophysical Society 53rd Annual Meeting
  Poster: "Coarse-grained Simulations and AFM Nanoindentation Experiments on a Hepatitis B Virus Capsid" (Anton Arkhipov, Wouter H. Roos, Gijs J. L. Wuite, Klaus Schulten)
  Poster: "Microsecond-timescale Explicit Solvent Molecular Dynamics Simulation of Protein Folding" (Peter Freddolino, Feng Liu, Sanghyun Park, Martin Gruebele, Benoit Roux, Klaus Schulten)
  Poster: "Atomic Scale Description of Ionic Behavior in Polymer Nanopores" (Eduardo R.Cruz-Chu, Klaus Schulten)
  Poster: "Calculation of Gating Charge in Kv1.2 Potassium Channel" (Fatemeh Khalili-Araghi, V. Jogini, V. Yarov-Yarovoy, Emad Tajkhorshid, Benoit Roux, Klaus Schulten)
  Lecture: "Simulations of Membrane Sculpting by N-BAR Domains" (Ying Yin, Anton Arkhipov and Klaus Schulten) Presentation: "The Computational Microscope" (Anton Arkhipov, Ying Yin, James Gumbart)

Lecture: "Regulation of the Protein-Conducting Channel by a Bound Ribosome" (James Gumbart)

- February 2009, Urbana, IL, University of Illinois, Center for the Physics of Living Cells, Post-doc and Graduate Student Symposium, "Single-molecule Studies of the Ribosome In Vitro and In Silico" (Leonardo Trabuco)

- January 2009, Urbana, IL, National Center for Supercomputing Applications, IACAT Accelerator Workshop
  Lecture: "Adapting a Message-Driven Parallel Application to GPU-Accelerated Clusters" (Jim Phillips)
  Lecture: "New Breakthroughs in NAMD/VMD and Quantum Chemistry CUDA Development and Useful Infrastructure Code" (John Stone, Jim Phillips, Dave Hardy, Jan Saam, and Klaus Schulten)

- November 2008, Austin, TX, ACM/IEEE, Supercomputing 2008 Conference (SC08)
  Tutorial Lecture: "High Performance Computing with CUDA: Molecular Dynamics" (Jim Phillips)
  Tutorial Lecture: "Molecular Visualization and Analysis" (John Stone)
  Technical Paper Lecture: "Adapting a Message-Driven Parallel Application to GPU-Accelerated Clusters" (Jim Phillips)

- November 2008, Urbana, IL, University of Illinois, ECE 598SP: Massively Parallel Processors Lecture: "GPU Computing Case Study: Molecular Modeling Applications" (John Stone)

- November 2008, Urbana, IL, University of Illinois at Urbana-Champaign, Cell and Molecular Biology & Molecular Biophysics Training Grants - 21st Annual Research Symposium, "Merging Data from Cryo-EM and X-ray Crystallography to Reveal Biomolecular Function" (Leonardo Trabuco)

- October 2008, Cape Town, South Africa, Cape Linux Users Group, "GPU Computing" (John Stone)

- October 2008, Cape Town, South Africa, CSIR Rosebank Campus, Centre for High Performance Computing
  Lecture: "Visualizing Biomolecular Complexes with VMD" (John Stone)
  Lecture: "An Introduction to Molecular Visualization with VMD" (John Stone)

- October 2008, Cape Town, South Africa, University of Cape Town, Computer Science Department, "Accelerating Molecular Modeling Applications with Graphics Processors" (John Stone)

- October 2008, Urbana, IL, University of Illinois at Urbana-Champaign, Beckman Institute Student Seminar Series, "Ribosome-induced Changes in EF-Tu Conformation Control GTP Hydrolysis" (Leonardo Trabuco)
- September 2008, Cold Spring Harbor, NY, Cold Spring Harbor Laboratory, CSHL Meeting on Translational Control, "Ribosome-induced Changes in EF-Tu Conformation: Mechanism of GTP Hydrolysis" (Elizabeth Villa)
- September 2008, San Francisco, CA, American Society for Cell Biology, "Ribosome-induced Changes in EF-Tu Conformation: Mechanism of GTP Hydrolysis" (Elizabeth Villa)
- September 2008, Lausanne, Switzerland, Centre Europen de Calcul Atomique et Molculaire Workshop, Membrane Protein Assembly: Theory and Experiment, "Bending of the Chromatophore Membrane Through Core Complex Dimerization: A Molecular Dynamics and Electron Microscopy Investigation" (Jen Hsin)
- August 2008, San Jose, CA, NVISION 2008. "Accelerating Computational Biology by 100x Using CUDA" (John Stone)
- August 2008, Urbana, IL, National Center for Supercomputing Applications, VSCSE: Accelerators for Science and Engineering Applications: GPUs and Multicore, "Case Study - Accelerating Molecular Dynamics Experimentation" (John Stone)
- August 2008, Philadelphia, PA, University of Pennsylvania, Center of Molecular Modeling, Workshop on QM/MM Simulations, "QM/MM in NAMD" (Chris Harrison)
- August, 2008, Osaka, Japan, XXI Congress of the International Union of Crystallography, Interface between Cryo-EM and Crystallography Microsymposium, "Merging Data from Different Resolutions to Reveal Biomolecular Function" (Elizabeth Villa)
- June 2008, Dresden, Germany, International Supercomputing Conference (ISC08), "Accelerating Molecular Modeling with Graphics Processors" (Jim Phillips)
- June 2008, Urbana, IL, National Center for Supercomputing Applications, Workshop on Programming Massively Parallel Processors, "Accelerating Scientific Applications with GPUs" (John Stone)
- June 2008, Arlington, VA, TeraGrid '08 Conference, "Long Time and Large Size Molecular Dynamics Simulations Made Feasible through New TeraGrid Hardware and Software" (Kirby Vandivort)
- May 2008, Boulder, CO, Linux Clusters Institute Conference, "GPU Acceleration of Molecular Modeling Applications" (Jim Phillips, John Stone)

Media Coverage

Stories involving the Resource appeared in popular media, online news sources, and other outlets over the last year. One popular story was about NVIDIA, a corporate leader in visual computing technologies, partnering with the Resource to open the very first CUDA Center of Excellence on the University of Illinois at Urbana-Champaign campus[‡]. The first simulation of the binding of molecules to a protein as carried out by Resource members was another popular story[§] In another example of media coverage, Resource Director Klaus Schulten was interviewed by the journal *Biomedical Computation Review*[¶] about successful software development and dissemination strategies.

All news-making stories and their reprints are documented by the Resource at the "In the News" section of the web site[‖]:

- Kloeppel, James. E. (April 14, 2009). Researchers study signaling networks that set up genetic code. *University of Illinois News Bureau*.
  http://news.illinois.edu/news/09/0414pathways.html
  Reprint:
  - Staff. (April 14, 2009). Researchers study signaling networks that set up genetic code. *EurekAlert!*.
    http://news.illinois.edu/news/09/0414pathways.html
- Wilson, E. K. (April 13, 2009). The looming petascale. Chemists gear up for a new generation of supercomputers. *Chemical & Engineering News*.
  http://pubs.acs.org/cen/science/87/8715sci3.html
- Baker, J. (February 16, 2009). Supercomputing means better models of earthquakes, cells and the universe. *Medill Reports*.
  http://news.medill.northwestern.edu/chicago/news.aspx?id=116329
- Staff. (February 4, 2009). NCSA Sponsors Panel, Showcases Visualizations at AAAS. *HPCWire*.
  http://www.hpcwire.com/offthewire/NCSA-Sponsors-Panel-Showcases-Visualizations-at-AAAS-39048092.html

[‡] http://www.nvidia.com/object/io_1214807636303.html

[§] http://news.illinois.edu/news/08/0630atp.html

[¶] http://www.biomedicalcomputationreview.org/5/1/7.pdf

[‖] http://www.ks.uiuc.edu/Publications/stories.cgi

- Stackpole, B. (January 23, 2009). Supercomputing Hits the Desktop. *Design News*. http://www.designnews.com/article/162620-Supercomputing_Hits_the_Desktop.php
- Sainani, K. (January 12, 2009). Tool dissemination - doing it right. *Biomedical Computation Review*, Winter 2008/2009, pp. 21-28. http://www.biomedicalcomputationreview.org/5/1/7.pdf
- Sinclair, G. (December 17, 2008). Ion channel simulations and free energy calculations on the grid. *iSGTW - International Science Grid This Week*. http://www.isgtw.org/?pid=1001556
- Wood, P. (November 21, 2008). UI researchers using genetic relationships to track evolution. *The News-Gazette*. http://www.news-gazette.com/news/local/2008/11/16/ui_researchers_using_genetic_relationships_to_track_evolution
- Staff. (October 22, 2008). Image of the week - Molecular dynamics on DEISA: lipids, licorice and lines.. *ISGTW International Science Grid*. http://www.isgtw.org/?pid=1001444
- Jakobsson, A. (October 14, 2008). PRACE investigated application requirements. *Innovations Report*. http://www.innovations-report.de/html/berichte/informationstechnologie/prace_investigated_application_requirements_120193.html
- Barker, T. (August 19, 2008). Powering new discoveries. *NCSA News*. http://www.ncsa.uiuc.edu/News/Stories/Poweringdiscoveries/
- Staff. (July 3, 2008). UC San Diego researchers identify potential new drug candidates to combat 'bird flu'. *e!ScienceNews.com*. http://esciencenews.com/articles/2008/07/02/uc.san.diego.researchers.identify.potential.new.drug.candidates.combat.bird.flu
- Staff. (June 30, 2008). NVIDIA Appoints First CUDA Center of Excellence. *NVIDIA.com*. http://www.nvidia.com/object/io_1214807636303.html
  Reprints:
  - Staff. (June 30, 2008). NVIDIA Appoints First CUDA Center of Excellence. *TradingMarkets.com*. http://www.tradingmarkets.com/.site/news/Stock%20News/1724385/
  - Staff. (July 1, 2008). NVIDIA Appoints First CUDA Center of Excellence. *Forbes.com*.

http://www.forbes.com/prnewswire/feeds/prnewswire/2008/06/30/prnewswire200806301230PR_NEWS_USPR_____AQM113.html

- Evans, J. (July 1, 2008). Nvidia appoints first CUDA centre of excellence. *Macworld (UK)*. http://www.macworld.co.uk/news/index.cfm?newsid=21856
- Meagher, S. (July 1, 2008). Nvidia gives university Cuda stamp of approval. *The Inquirer.net*. http://www.theinquirer.net/gb/inquirer/news/2008/07/01/nvidia-appoints-first-cuda
- Williams, I. (July 2, 2008). Nvidia appoints first Cuda centre of excellence. *vnunet.com*. http://www.vnunet.com/vnunet/news/2220531/nvidia-appoints-first-cuda-centre
- Fussy, C. (July 2, 2008). Nvidia approuve Urbana Champaign comme centre de dveloppement Cuda. *TheInquirer.fr*. http://www.theinquirer.fr/2008/07/02/nvidia_approuve_urbana_champaign_comme_centre_de_developpement_cuda.html
- Staff. (July 2, 2008). Nvidia nomina il primo centro di eccellenza CUDA. *amdplanet.it*. http://www.amdplanet.it/tag/nvidia/news/20593/nvidia-nomina-il-primo-centro-di-eccellenza-cuda.html
- Staff. (July 3, 2008). NVIDIA desemneaza primul centru de excelenta CUDA. *BURSA.ro*. http://www.bursa.ro/on-line/s=international&articol=29523.html
- Staff. (July 15, 2008). NVIDIA selects UIUC as first CUDA Center of Excellence. *EFYTimes.com*. http://www.efytimes.com/efytimes/27517/news.htm
- Staff. (July 22, 2008). Nvidia nombra el primer Centro CUDA de excelencia. *DiarioTi.com*. http://www.diarioti.com/gate/n.php?id=18560

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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 18 visitors provided with 69 demonstrations during the May 2008 – April 2009 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 party will request multiple images or movies. From May 2008 – April 2009, 66 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. Established in October 2007, the site currently contains a library of 13 Resource 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 (using the Creative Commons[§] framework) requires that the Resource

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

[††] `http://www.ks.uiuc.edu/Gallery/Movies/`

[†] `http://www.youtube.com/tcbguiuc`

[‡] `http://www.youtube.com`

[§] `http://creativecommons.org`

be acknowledged when the movie is used, and that commercial use and derivative works are prohibited.

As of April 2009, the most viewed movies were "Water Channels in Cell Membranes"[¶] with 7,189 views, and "Lipoproteins that Circulate in the Blood Collecting Fat"[‖] with 7,020 views. The total count of all views of all listed videos since the gallery was started reached to around 29,000 views as of April 2009.

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. In the last 12 months, the Resource has had license inquiries from an overseas computer manufacturer and a major pharmaceutical company, and is currrently working to resolve those requests. Further, the Resource is working to fill a staff position created for the Resource in concert with the University of Illinois Office of the Vice Chancellor of Research where responsibilities would include developing licenses for and marketing Resource software to the private sector.

[¶] `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, hosting visitors, teaching classes, and graduate training. 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:

- A tutorial session reaching 170 attendees, and launch of two workshops
- Nearly 66,000 views of all online tutorials
- Release of the *Membrane Proteins* and *Shape-Based Coarse Graining* tutorials
- Updates to Resource tutorials
- Nearly 6,000 views of online case studies
- Nine participants in the Resource's Visitor Program
- Doctoral and postdoctoral training
- Graduate and undergraduate classes taught by Resource faculty

Tutorial Session and Workshops

At the SC08 International Conference for High Performance Computing, Networking, Storage and Analysis, held November 15-17, 2008 in Austin, Texas, Resource Senior Research Programmers John Stone and Jim Phillips joined with collaborators from NVIDIA to present a one-day tutorial session titled "M02: High Performance Computing with CUDA"*. The tutorial session provided attendees with an overview of CUDA†, NVIDIA's general purpose scalable parallel programming model for writing highly parallel applications, with Resource members Stone and Phillips providing examples of CUDA codes developed in Resource software. Attendance at the tutorial session was high, with 170 attendees. Evaluation results from post-event participant surveys are high overall, and across specific items like lecture quality, presenter knowledge, and technical content. Nearly all attendees - over 98% - indicated that they would like to see the tutorial session repeated at the next supercomputing conference.

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*`http://sc08.supercomputing.org/scyourway/conference/view/tut109.html`

†`http://www.nvidia.com/cuda`

Over the last year the Resource organized and is currently reviewing applications for two hands-on workshops to be held in Summer 2009, on July 6-10[‡] and again on August 10-14[§] in Champaign, Illinois. A continuation of the Resource's highly successful workshop program[¶], these five-day workshops will explore physical models and computational approaches used for the simulation of biological systems and the investigation of their function at an atomic level. The workshops will utilize examples including the properties of membranes and membrane proteins, mechanisms of molecular motors, and conduction through water and ion channels. Relevant physical concepts, mathematical techniques, and computational methods will be introduced, including force fields and algorithms used in molecular modeling, molecular dynamics simulations on parallel computers, and steered molecular dynamics simulations. 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. Theory sessions in the morning will be followed by hands-on computer labs in the afternoon in which students will be able to set up and run simulations.

Tutorials

The Resource maintains and updates a library of tutorials for use in self-study by the biomedical community. 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. Two new tutorials, described below, were added over the last 12 months:

- *Membrane Proteins Tutorial* - Added by the Resource in February 2009, *Membrane Proteins* is a step-by-step tutorial for setting up and running molecular dynamics simulations of membrane proteins. The tutorial is subdivided into three separate units: The first unit covers steps required to set up a structural model of a membrane protein starting from a raw PDB file; the second unit describes the steps needed to place the protein in a native-like membrane environment; and, the third unit describes the steps required to minimize and equilibrate the resulting system with NAMD.
- *Shape-Based Coarse Graining* - Coarse-graining (CG) refers to making a simplified model of a molecular system, e.g., reducing groups of atoms to point masses

[‡] `http://www.ks.uiuc.edu/Training/Workshop/Champaign09J/`

[§] `http://www.ks.uiuc.edu/Training/Workshop/Champaign09A/`

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

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

(beads). Posted in May 2009, this tutorial presents one method of coarse-graining, called shape-based coarse-graining, which has been quite successful in a number of applications. In this method, a small number of CG beads are used to represent overall shapes of proteins or lipid membranes, with typical ratio of 200-500 atoms per bead. The tutorial introduces tools for shape-based CG that are available in VMD via plugins.

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

Interest in the tutorials is high. As indicated by Resource web site statistics on views of the tutoral library, there were well over 65,000 views of all tutorials over the recent 12-month period. The 10 most popular tutorials in terms of online views are shown in Table 3, with the tutorials providing introductions to VMD and NAMD the most popular.

Ten Most Viewed Tutorials	Views
VMD Molecular Graphics	23,618
NAMD Tutorial	13,594
VMD Images and Movies	7,541
Building Gramicidin A	3,396
Simulation of Water Permeation through Nanotubes	2,571
Topology File Tutorial	2,396
Stretching Deca-Alanine	1,835
Aquaporins with the VMD MultiSeq Tool	1,796
Parameterizing a Novel Residue Windows	1,410
Alchemical Free Energy Perturbation Calculations in NAMD	1,283
Total for all tutorials	65,575

Table 3: Views of online tutorials from May 2008 - April 2009

Case Studies

Case studies consist of text (in PDF format) and associated files, are authored by the Resource, and are made available online for public download and use** at the Resource web site. From March 2008 - April 2009 there were nearly 6,000 views of the case studies, with the DNA and Membranes case studies the most popular, as shown in Table 4.

Case Study	Views
DNA	1,220
Membranes	836
Myoglobin	807
Water and Ice	669
Structure of Ion Channels	517
Ubiquitin	422
Titin Ig Domains	405
BPTI	381
Light Harvesting Complex II	370
Aquaporins	308
Total	5,935

Table 4: Views of case studies from May 2008 - April 2009

Visitor Program

The Resource visitor program provides scientists (who typically 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 2008 - April 2009 period (listed by the month they started their visit) include:

- Wen Li, Columbia University (April 2009)
- Ly Le, University of Utah (April 2009)
- Axel Kohlmeyer, University of Pennsylvania (April 2009)

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

- Eva Krammer, Universite Henri Poincare (March 2008)
- Christopher Chipot, Universite Henri Poincare (November 2008)
- Francois Dehez, Universite Henri Poincare (November 2008)
- Ilya Solov'yov, Johann Wolfgang Goethe University (September 2008)
- Paul McCreary, Evergreen State College (July 2008)
- Xueqing Zou, Peking University (October 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.

- Eric Lee, Biophysics, University of Illinois, Spring 2009
- Peter Freddolino, Biophysics, University of Illinois, Spring 2009
- James Gumbart, Physics, University of Illinois, Spring 2009
- Anton Arkhipov, Physics, Univesity of Illinois, Fall 2008
- Yi Wang, Biophysics, University of Illinois, Fall 2008

Postdoctoral Associates: Postdoctoral associates that have recently received or are currently receiving training at the Resource over the last 12 months are:

- Anton Arkhipov
- David Hardy
- Chris Harrison
- Barry Isralewitz
- Eric Lee
- Jan Saam
- Eduard Schreiner
- Melih Sener

- 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 2008 - Spring 2009 are listed below.

- Biomolecular Physics
- Statistical Physics
- Physical Chemistry
- Special Topics in Physics

Resource Library

The Resource library, an important internal training resource, has been expanded by the purchase of 43 new books, bringing the total volume count to 1,043 volumes. Further, to supplement the UIUC librarys collection of on-line and print journals, the Resource receives the following journals in science and computing: *Physics Today*, *Science*, and *Nature*.

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