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

Contents

General Description of Resource Operation:

The 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 is supported by an outstanding technical staff with many years of experience and technological contributions that make them as highly regarded as the Resources faculty leaders.

The two main Resource software programs are VMD (Visual Molecular Dynamics) and NAMD (Nanoscale Molecular Dynamics). A key computational methodology developed and furnished by the Resource is molecular dynamics flexible fitting (MDFF) for the multi-modal (X-ray and electron microscopy) analysis of large structures. The Resource continued also the development of special computational solutions for bionanotechnology and other biomedical areas, focussing lately on serving membrane protein research. Resource projects build on these tools and demonstrate to the scientific community advances made possible through computational means. The Resource improves its tools continuously through a unique interdisciplinary approach that brings together physical, computational and biomedical scientist.

Four core development areas of the Resource focus on (1) on the development of the general sequence, structure, and modeling tool VMD (Visual Molecular Dynamics), (2) on the development of the Molecular Dynamics Program (NAMD), (3) structural systems biology based on MDFF, and (4) providing area specific tools in bionanotechnology, membrane protein studies and other fields. The Resource is very active in hands-on training of computational biomedicine and operates a popular website 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. Users of the software are provided with extensive training in the mentioned hands-on workshops and responsive service through email. The Resource software, that is distributed free of charge, is being used by biomedical scientists from the bench to the worlds most outstanding computer centers every day, while high school, college, and graduate students utilize training and visualization material to discover for themselves the miracle of living cells.

The Resource is presently involved in several outstanding biomedical research projects: battling drug resistance in the swine flu virus (H1N1); resolving the action of the ribosome in chemical detail to advance drug design for antibiotics; fighting coronary diseases by advancing knowledge on cholesterol uptake by high density lipoporoteins and on bloodclotting factors, learning the molecular fundamentals of muscle stretching, and perfecting DNA sequencing for personalized medicine. In addition, the Resource is engaged in groundbreaking research at major frontiers of cell biology, from showing the folding process of proteins at an atomistic level, to investigating how photosynthetic organisms

harvest light and convert it into chemical energy, and to providing images of how living cells shape their interior membranes.

The operation of the resource hinges on its people. Faculty, postdocs, and students from departments of physics, chemistry, and biochemistry engage in the most challenging research problems through collaborations with experimental laboratories. The projects have been selected for their great scientific potential and since they require fundamental advances of the available software tools, new algorithmic strategies, and even entirely new theoretical concepts. The Resource is closely linked to two major research efforts, the NSF funded Center for the Physics of Living Cells (co-directed by K. Schulten) and the NIH funded glue grant for membrane processes.

The Resource software development team has a long history of close collaborations that take advantage of new commodity technologies as well as leading edge technology, presently, the use of graphics processing units for general purpose computing and the use of the upcoming, NSF funded Blue Waters petascale computer on which the Resource program NAMD will be a key application. 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 scientist and strategies from computational scientists into modern software code that is continuously adapted to available and near term computational resources. On the one hand, the Resource has developed a superbly functioning team on the other hand it continues 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.

VMD. This core develops the software package VMD. The package has been improved with many new features and on August 1st 2009 VMD 1.8.7 was officially released to the public. The main improvements of the last year consist of GPU-accelerated algorithms in VMD, extending them to support parallel execution on multi-GPU workstations increasing performance by up to a factor of 8 over a single GPU. The GPU algorithms in VMD increase the performance for computational tasks such as calculation of electrostatic fields and computation and display of molecular orbitals for visualization of quantum chemistry simulation. Another big challenge of this year was to adapt VMD to the computational demands of analyses of petascale molecular dynamics simulations that become possible in 2011. To this end VMD was refined to support execution on clusters and supercomputers using MPI (Message Passing Interface). The new MPI-enabled builds of VMD furnish several parallel reduction primitives that allow researchers to write parallel analysis scripts without having to learn MPI or otherwise become experts in parallel programming. Complex molecular dynamics trajectory analyses can now be accomplished in much less time than was previously possible. Together with other updates of VMD it is now possible to

compute 100 million atom biomolecular complexes.

NAMD. The Nanoscale Molecular Dynamics package is a parallel molecular dynamics code designed for high performance simulation of large biomolecular systems. It allows excellent parallel scaling on both massively parallel computers and commodity workstations. In November 2009 NAMD 2.7b2 was released and has been downloaded by over 4,200 users, 700 of who are NIH funded. This package furnishes refinement to the collective variable, free energy, and grid force methods introduced by its predecessor NAMD 2.7b1. This is the first release that sports graphics processor acceleration based on the CUDA technology from NVIDIA. Upcoming developments will target the new NVIDIA Fermi architecture, the first with a shared cache, and will add compatibility with the alchemical free energy methods currently only supported in the CPU version. In addition, NAMD 2.7b2 also includes the option to use a compressed molecular structure file format that considerably reduces the per-process memory needed to run large-scale molecular systems. All in all, this new version is more convenient and much higher in performance: it allows simulations such as the 100-million benchmark simulations for the NSF Blue Waters petascale machine.

Structural Systems Biology with MDFF. Last years start of the NSF "Center for the Physics of the Living Cell (CPLC) paved the way for even more fruitful research collaborations between University of Illinois faculty and the Resource. These collaborations help drive the Resources technology developments and led to new advances of the program packages VMD, NAMD, and MDFF. A key step forward was the development of MDFF, with its ability to combine electron microscopy and X-ray data. MDFF has been successfully applied to gain more insight into how the ribosome works which will help in the design of better antibiotics. Resource scientists collaborate with several leading electron microscopy laboratories, which are applying MDFF to a wide variety of systems thereby driving further the development of the method. Also at the forefront of cell biology research is the investigation into the protein-conducting channel (SecY) that is responsible for integrating proteins into the cell membrane enabling cells to express a myriad of proteins on its cell surface. The advancements in the VMD and NAMD programs make it now possible to simulate whole systems like a ribosome-SecY-membrane complex or the chromatophore, a multi-protein light-harvesting complex of photosynthetic organisms, reaching the goal of simulating macromolecular complexes of up to 100 million atoms. Resource scientists also developed a model for the dynamics of membrane sculpting by so-called BAR-domains, another great challenge to the computational power of the Resource, since it requires a simulation of up to 100 million atoms over many microseconds (this goal was reached in a multi-scale modeling approach).

Bionanotechnology and Membrane Protein Studies. Experimental methods cannot reach to the nanoscale where biological processes take place. This gap can now be filled by computational methods that can simulate those processes at an atomistic level. The use of these methods is particularly relevant in bionanotechnology and membrane protein studies. Molecular dynamics simulations carried out at the Resource guided the development of nanosensors to measure methylation profiles of DNA, to describe voltage gating of ion channels and even the insertion of nascent protein resolved in a ribosome-SecY complex into a membrane.

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 13 joint publications in the last year through these collaborations, with 10 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 24,800, for NAMD by 6,300, and 617 new users registered for BioCoRE. User support continued, with for example, 4,500 exchanges sent to the VMD support email address. Over the last year 12 visitors received training at the Resources visitor center, and 15 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 12 months (July 6-10 and August 10-14, 2009) the Resource organized two one-week hands-on workshops at its home base of Urbana-Champaign, Illinois. Local, national, and international participants attending the workshop experienced morning conceptual lectures followed by afternoon hands-on tutorial sessions on their laptops, configured with Resource software. Evaluation results indicate that across both workshops 92% of participants felt the events broadened their understanding of concepts and principles in the field of computational and theoretical biophysics. Further, Resource members provided one day of lectures and tutorials for a Cryo-EM Workshop, held January 14-17, 2010, and organized by the National Center for

Macromolecular Imaging at Houston, and Resource software and tutorials provided the foundation for a November 23-26, 2009 Workshop on Molecular Simulation of Bio and Nano Particles organized by the University of Talca in Chile. Two new tutorials, *Molecular Dynamics Flexible Fitting* and *Structure Check* were also posted by the Resource on its website for public consumption. Interest in Resource online training materials is high, with over 81,000 views of Resource tutorials and case studies in the past 12 months. Currently the Resource is organizing more workshops, both locally and at locations in Pittsburgh, San Diego, and Atlanta.

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 796,000 unique visitors to its web site, resulting in 3.0 terabytes of information transfer; the visitors downloaded over 17,400 publications from the Resource's online publications database. Dissemination also prospered in more traditional academic activities, including 43 articles in refereed journals or other publications (with 11 more in press), 60 talks by Resource PIs and 29 presentations by others; and 45 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

On The Path to Petascale Biomolecular Simulations (SPID 0075)

The 2006 National Science Foundation solicitation *Leadership-Class System Acquisition—Creating a Petascale Computing Environment for Science and Engineering*[*] specified as a model problem a molecular dynamics simulation of 100 million atoms performed with the Resource's popular, highly parallel simulation program NAMD.[†] With the awarding of the IBM Blue Waters[‡] system, to be installed at the University of Illinois in 2011, the dream of petascale biomolecular simulations became a milestone for the Resource. As the 100-million-atom model problem is an acceptance test for the machine, the Resource is receiving unprecedented levels of assistance in preparing NAMD to run reliably and efficiently. Molecular dynamics with NAMD is one of five "NSF Challenges" around which Petascale Application Collaboration Teams have been formed.

The Resource has been competitively awarded one of the first Petascale Computing Resource Allocations for its proposal *The Computational Microscope*. The Resource will employ Blue Waters to explore the following four processes:

- **Protein elongation in the ribosome**, in collaboration with Joachim Frank (Columbia U., HHMI), a pioneer in cryo-EM and ribosome structure determination, and Taekjip Ha (U. Illinois, HHMI), a leader in single-molecule studies. A dynamic, atomic-level description of conformational changes and catalytic factor binding by the ribosome during DNA-to-protein translation is crucial to understanding its function and for the development of new antibiotics.

- **Structural transitions in poliovirus entry**, in collaboration with James Hogle (Harvard U.) and Xiaowei Zhuang (Harvard U.). Fighting viral infections is difficult as few anti-viral drugs exist and usually only preventive measures are available, such as vaccination. The poliovirus infection process is representative of viruses causing hepatitis A, the common cold, and viral meningitis. Resolving its infection process in chemical detail may offer new opportunities for pharmacological interventions.

- **Sculpting cellular membranes by BAR domains**, in collaboration with W. Cho (U. Illinois Chicago). Reshaping the structure of cellular membranes is crucial for cell growth, function and communication, but it is still largely unknown how the intricate shapes of intra-cellular structures and organelles are built and maintained. These simulations will show how BAR domain protein lattice formation on the membrane surface induces membrane tubulation.

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[*]URL: `http://www.nsf.gov/pubs/2006/nsf06573/nsf06573.html`

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

[‡]URL: `http://www.ncsa.illinois.edu/BlueWaters/`

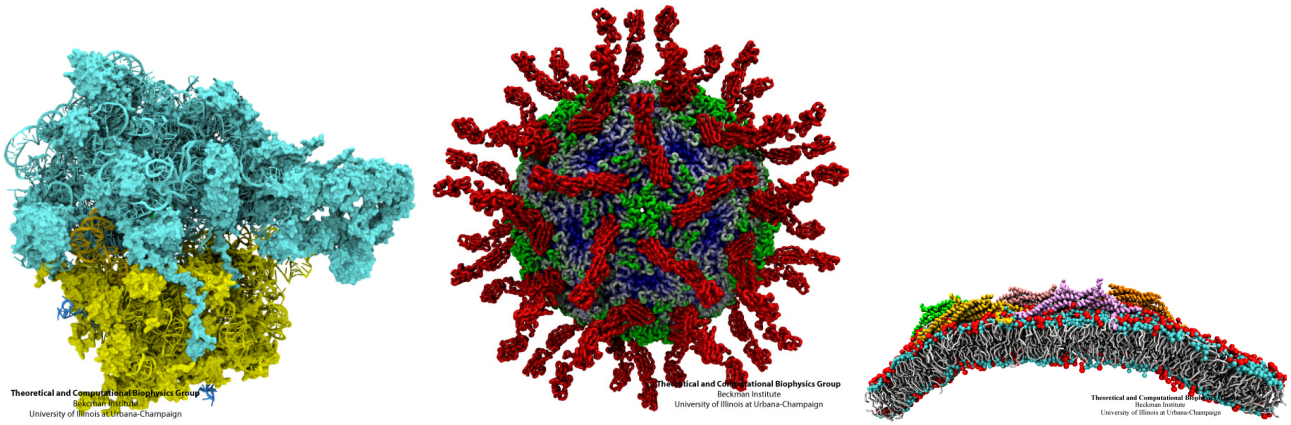

Figure 1: Ribosome, poliovirus, and BAR domain petascale simulation targets.

- **Energy conversion by the chromatophore organelle**, in collaboration with C. N. Hunter (U. Sheffield). Life on earth depends on sunlight harvested by photosynthetic life forms, which may guide technological innovations in solar power production or be directly exploited to produce fuels such as hydrogen gas photosynthetically. The chromatophore is one of the simplest organelles found in cells capable of turning sunlight into chemical fuel.

These collaborative projects will stretch the capabilities of the Resource at every level. In order to locally store, analyze, and visualize the massive data produced by petascale simulations, the Resource was competitively awarded an NIH small equipment grant to assemble a "Petascale Molecular Dynamics Data Processing System" with over 200 terabytes of storage, graphics-processor-accelerated compute servers, and a large-memory, ultra-high-resolution visualization system.

The required modifications to both NAMD and the Resource's most popular product, the simulation preparation, visualization, and analysis program VMD,[§] are well under way. A new binary file format for efficiently storing and accessing 100-million-atom molecular structures has been implemented as a VMD molfile plugin. NAMD can read this format and compress the bonding structure by identifying common repeated structures, greatly reducing the static replicated data that is stored on every node. NAMD reads the remaining per-atom data using dedicated input/output threads scattered across the machine, which also write the trajectory output file. A new load balancer is similarly distributed and hierarchical. Finally, VMD has been extended with a message-passing interface to allow user-written scripts to easily coordinate distributed calculations.

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

Petascale Molecular Dynamics Data Processing System (SPID 0073)

Biomedically-relevant cell-scale processes take place in molecular assemblies made of millions to hundreds of millions of atoms. Atomistic molecular dynamics (MD) simulation of these structures provides insight into their functional mechanisms; such simulations are extremely demanding and require petascale computational resources.

The University of Illinois at Urbana-Champaign campus has won the NSF competition for a new petascale machine that will be the single largest and fastest computer at all NSF centers promising a speed-up in computational capacity by a factor 100 over present machines. The machine, Blue Waters operated by NCSA, will cost in excess of $216 million in addition to $150 million of additional infrastructure. The new machine, to be installed 2011/2012 will place UIUC at the forefront of computational science and engineering in general, and, in particular, at the forefront of computational biomedicine.

Traditional terascale molecular dynamics data, generated from 50 ns, 100,000-atom MD simulations, requires 60 GB of storage and, following common data-reduction practices, is practical to work with using today's workstations. The 5 μs, 1 million-atom simulations achievable with a petascale supercomputer (e.g. Blue Waters), requires 60 TB of memory, resulting in a thousand-fold increase in storage, analysis, and visualization requirements; the Petascale MDDPS meets these requirements.

Petascale datasets are so large that existing workstations are too limited to efficiently handle them. There are losses in performance as data size exceedes the limit of a resource: a dataset too large to fit into physical memory (RAM) must be read from the computer's local disk hundreds of times more slowly than from physical memory. Furthermore, a dataset too large to fit into local disk would need to be fetched from a remote site, such as a supercomputer center's mass storage system, which is yet hundreds of times slower than from local disk; such transfers take hours to days to complete. Common visualization tasks, such as calculating three-dimensional electrostatic potential maps across a trajectory, can take minutes or longer using a standard desktop workstation, inserting multiple prolonged interruptions into what should be interactive visualization. As a result of such limitations, a researcher's analysis of a large simulation result is slowed so much as to be virtually impossible. The Petascale MDDPS is designed to overcome the shortcomings of desktop computer workstations and to provide the necessary hardware features to enable analysis and visualization of challenging petascale datasets.

The Petascale MDDPS, shown in Fig. 2, is a cluster of tightly coupled computers that operate as a cohesive unit to provide high-performance data analysis capabilities required by intra- and extra-mural UIUC NIH research projects, complementing the hardware available at the NSF supercomputing centers on campus (National Center for Supercom-

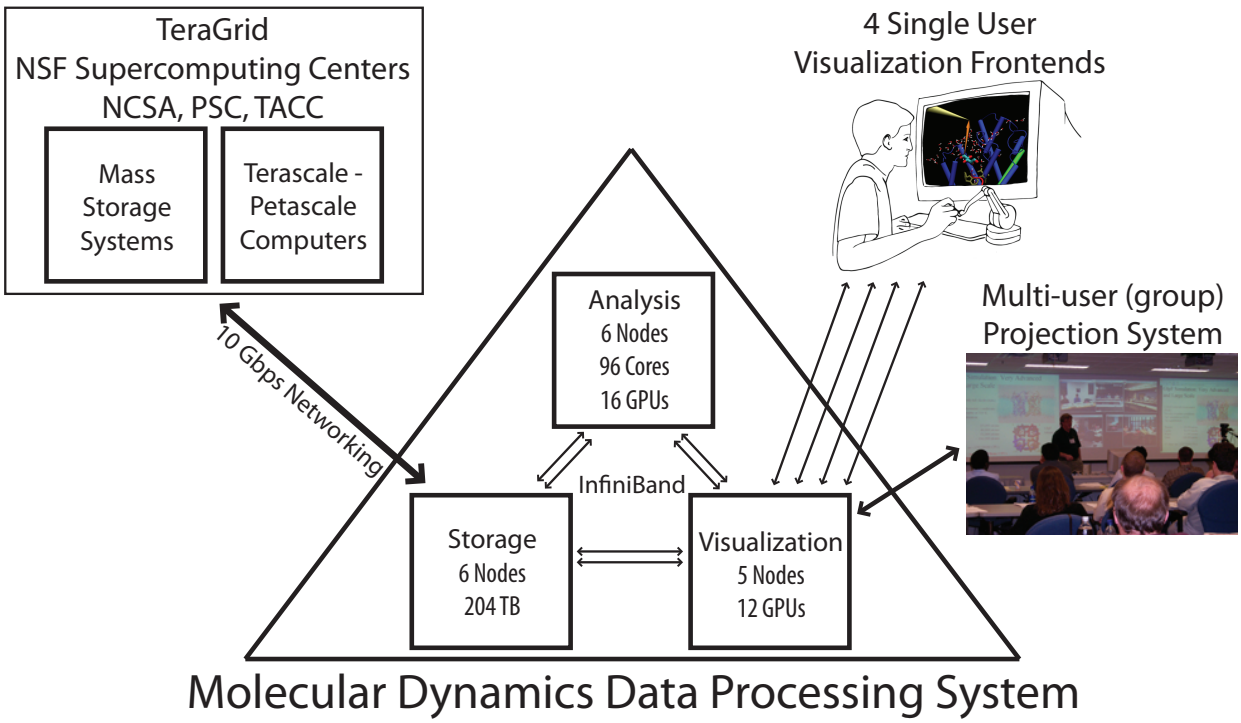

Figure 2: Overview of the Petascale MDDPS.

puting Applications) and elsewhere (Pittsburgh Supercomputing Center, Texas Advanced Computing Center). The system is composed of synergistic storage, analysis, and visualization nodes connected internally and to external resources by separate high-speed networks. Each of the nodes composing the system is selected from commodity off-the-shelf (COTS) server hardware. What makes the system uniquely capable is the particular combination of nodes and the way they are integrated into a functional whole.

While both of the Resource's software packages, NAMD and VMD, are well-tuned to current computer hardware, harnessing the next-generation capabilities of the Petascale MDDPS hardware requires additional software development. NAMD's already-superb scaling to large numbers of processors will be improved to take advantage of Blue Waters 100-fold increase in processing power. VMD will be extended to provide increased GPU support and improved efficiency when used in parallel computing environments such as clusters and many-core processing nodes. The thousand-fold increase in required storage also demands the file-handling components of NAMD and VMD to be enhanced as well.

Understanding antiviral drug resistance mechanisms of H5N1 "avian" and H1N1pdm "swine" influenza virus. (SPID 0074)

The recent outbreak of the H1N1pdm "swine" influenza caught not only its victims by surprise, but also biologists who had assumed that the virulence (and ultimately, lethality) of human flu viruses were generally limited to the elderly and immunocompromised. Most fatal cases of H1N1pdm, however, involved young previously healthy people, raising the possiblity that H1N1pdm could eventually mutate into a strain capable of killing even healthy individuals, such as in the 1918 flu pandemic where an estimated 50 to 100 million people died (approximately 3% of the 1.6 billion population at the time). Even more alarming however, was that while the intiial strains of H1N1pdm appeared to be susceptible to conventional antiviral therapy, the strain has mutated quickly to become drug-resistant to the front line antiviral drug, oseltamivir (Tamiflu). Oseltamivir normally functions by binding to the flu protein neuraminidase and preventing the virus from budding out of its host cell after replication. This alarming discovery, that the virus has gained an upper hand on medicine, has raised grave concerns regarding an effective defense against subsequent influenza outbreaks.

The H1N1pdm "swine" influenza virus is closely related to the 2003 H5N1 "avian" influenza virus for which oseltamivir-resistance due to two individual point mutations, H274Y and N294S, is well known. However, the mechanism behind why these mutations actually inhibit successful binding of oseltamivir to neuraminidase is not well understood. Furthermore the mutations are actually located some distance from the drug-protein binding site, suggesting that the mutations may disrupt the actual drug binding process rather than just forming an inhospitable environment for drug-protein endpoint interactions. The goal of our study was therefore to model and simulate the binding of oseltamivir to H1N1pdm and H5N1 neuraminidase proteins, in order to a) understand at the molecular level what role these point mutations play in drug-resistance, and b) employ our findings to suggest strategies for designing drugs that can circumvent the virus' resistance mechanisms.

A new development by the Resource which assisted this investigation is that of a GPU-accelerated version of the multilevel summation method [1], which permitted the practical calculation of electrostatic potentials necessary to map the charged interaction surfaces between drug and protein across long simulation trajectories. This key application of cutting edge technology reduced the time required to analyze a large trajectory from months to hours. Our study also employed a variety of well known tools developed by the Resource, namely sequence analysis via Multiseq [2], molecular modeling and analysis using VMD [3], and high speed parallel computing employing NAMD [4].

Our simulations on both H1N1pdm and H5N1 neuraminidases shed light on two pre-

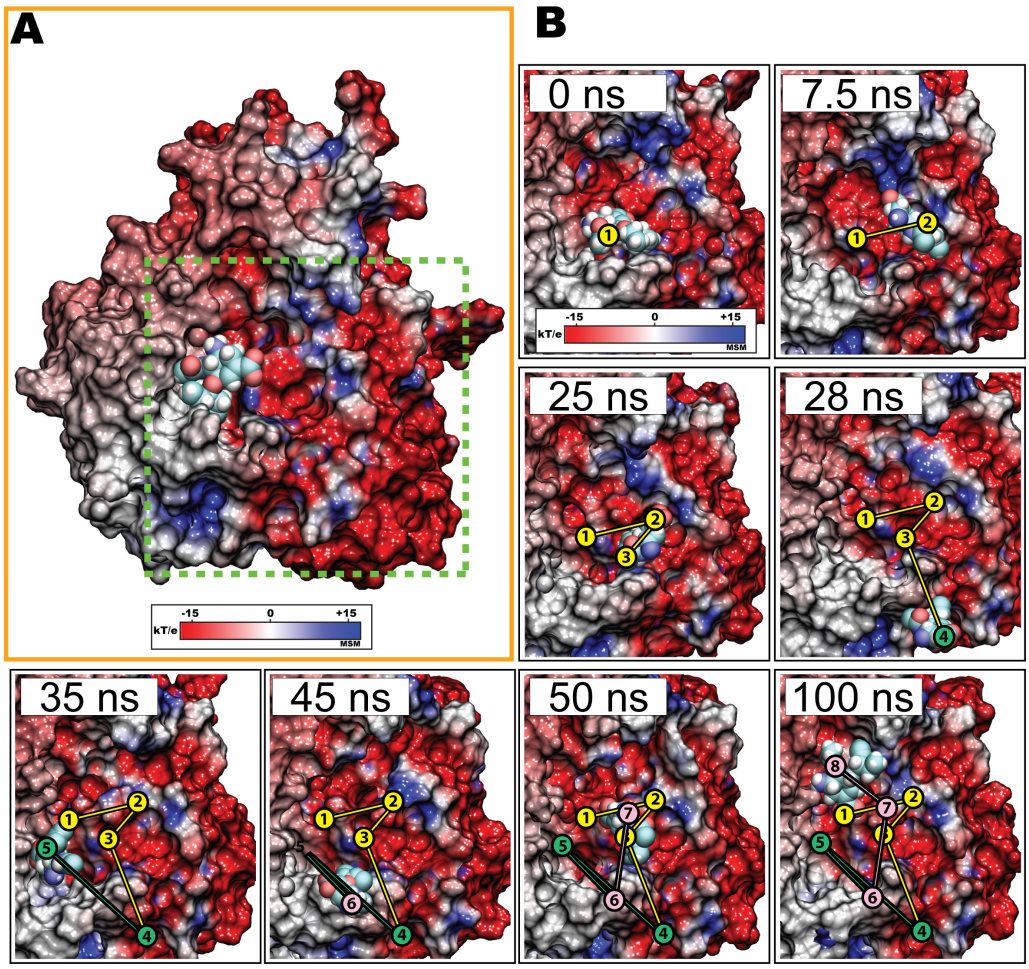

Figure 3: Mapping a drug binding pathway for oseltamivir on neuraminidase. Shown in A) is a simulated system involving H5N1 neuraminidase and oseltamivir. The surface of the protein is colored by electrostatic potential, clearly showing a negatively charged binding pathway for oseltamivir. In B), the escape and rebinding of oseltamivir through the electrostatic binding funnel can be seen in snapshots from a 100 ns long trajectory.

viously unknown properties of antiviral drug interaction with flu proteins. First, the simulations uncovered a negatively charged funnel through which oseltamivir is capable of binding into the central core of neuraminidase (shown in Fig 3A). We were fortunate, in fact, to capture and observe both the unbinding and rebinding of oseltamivir through this pathway in a long 100 ns simulation (shown in Fig 3B). Second, the simulations revealed two strategies the mutant flu strains employ to discourage the binding of oseltamivir. In the case of the H274Y mutation, our simulations showed that there was a disruption of a key hydrogen bond that stabilized oseltamivir within neuraminidase's active site, as well as a weakening of hydrophobic contacts between drug and protein. Our simulations suggest that the N294S mutation physically alters the local protein conformation along the charged binding pathway identified earlier, and therefore inhibits drug binding.

Our results demonstrate not only a viable pathway for the binding of an antiviral drug, but also how the disruption of such a pathway from known point mutations can function

as the basis for resistance to the front line anti-influenza drug oseltamivir. The discoveries from our initial simulations [5] should pave the way for designing drugs which can bind stably to flu neuraminidase despite disruption of H274Y hydrophobic and N294S pathway interactions.

Structural Analysis of the Ribosome (SPID 0042)

The ribosome is the protein factory present in all cells. Pieces of the DNA sequence are first transcribed into messenger RNA molecules, which are then read by the ribosome and translated into protein sequence. The ribosome is one of the largest and most complex molecular machines. Recent breakthroughts in the determination of atomic structures of the ribosome using X-ray crystallography culminated in the 2009 Nobel Chemistry prize. Due to its central biological role, the ribosome is a major target of antibiotics. Indeed, many antibiotics in clinical use block protein synthesis in the bacterial ribosome [6], exploiting differences between bacterial and human ribosomes.

Protein synthesis by the ribosome occurs in a multi-step fashion. The steps include decoding of the genetic information, incorporation of a new amino acid into the protein being synthesized, and movement of the messenger RNA through the ribosome, among others. At each of these steps the ribosome adopts different structures and interacts with a variety of auxiliary factors. Understanding of each step at the molecular level requires high-resolution structural information of the ribosome at intermediate states of protein synthesis. Several images of the ribosome at particular functional states are provided by electron microscopy. However, these images are at intermediate resolution, not enough to reveal exact positions of atoms. Hybrid computational methods can combine high-resolution, atomic structures furnished by X-ray crystallography with images of ribosomes at particular functional states provided by electron microscopy. With atomic models obtained using hybrid methods, important intermediate steps of protein synthesis can be studied with great detail [7].

The Resource developed the molecular dynamics flexible fitting (MDFF) method, which combines electron microscopy and X-ray data [8, 9].* MDFF morphs an atomic structure obtained by X-ray crystallography into a density map provided by electron microscopy. MDFF is built on top of the two main programs developed by the Resource, namely VMD [3] and NAMD [4]. MDFF has been successfully applied to study the ribosome [10–14], as well as protein-induced membrane curvature [15, 16]. Resource scientists collaborate with several leading electron microscopy laboratories, which are applying MDFF to different systems and driving further development of the method.

Certain proteins are able to regulate ribosome function while they are still being synthesized and reside the ribosome. In particular, there are several examples of nascent proteins that regulate gene expression by stalling protein synthesis. In collaboration with Roland Beckmann (U. Munich, Germany), a leader in structural analysis of the ribosome by electron microscopy, Resource scientists applied MDFF to obtain an atomic model

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

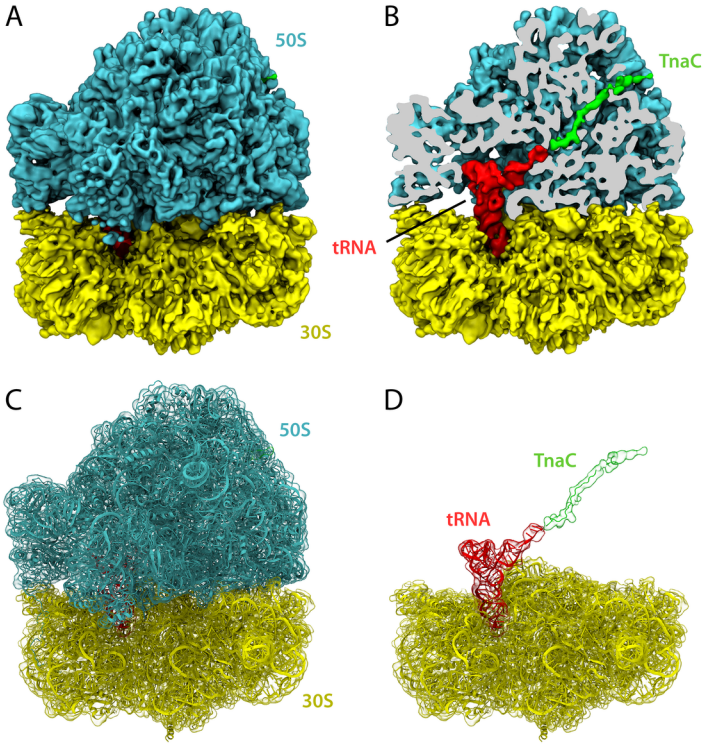

Figure 4: Structure of the ribosome stalled by the TnaC. (A,B) Electron microscopy image at 5.8 Å resolution. (C,D) Atomic model obtained by applying the MDFF method developed by the Resource.

of the ribosome stalled by a regulatory nascent chain called TnaC [13] (Fig. 4).[†]. The MDFF-derived atomic model revealed in detail the mechanism by which TnaC shuts down the ribosome. It was seen that key residues of the ribosome are positioned in such a way that release factors, responsible for terminating protein synthesis, cannot bind [13]. In a follow-up work, Resource scientists employed large-scale simulations and other computational techniques to determine how the TnaC sequence is specifically recognized by the ribosome [14].

MDFF has proven to be a power technique for merging multi-resolution structural data. Resource scientists are now applying it to investigate several other aspects of protein synthesis, such as the regulation of large-scale ribosomal motions critical for fidelity of protein synthesis. Structural analyses using MDFF 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 protein synthesis at the molecular level is of major interest to understanding the molecular biology of the cell. Furthermore, development of new antibiotics, much needed due to the constant emergence of resistant bacterial strains, stands to benefit greatly from the availability of atomic models of the ribosome at intermediate states of its function.

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

Membrane Protein Structural Dynamics Consortium

Membrane proteins play an essential role in controlling the movement of material and information in and out of living cells, in determining the flow and use of energy, and in triggering numerous signaling pathways. As such, they participate in almost all cellular processes fundamental to life, development, and well being of cells and organisms. Similar to all proteins, in order to fulfill their roles, membrane proteins undergo structural changes of varying nature and degree during their function. Such conformational changes determine, e.g., how a membrane transporter imports nutrients across the cellular membrane into the cell, how multi-drug resistance proteins pump drugs outside the cell and, thus, develop resistance in cancer cells, how channels involved in electrical activities of the heart and the brain open and close in response to neurotransmitters and hormones in the body, how various mutations of membrane proteins result in detriment effects in patients carrying them, and how interaction of membrane proteins with drugs might be used to correct and modify the physiological response of a human being. It is no wonder that membrane proteins are the most prominent class of targets in pharmacology of mammalian cells and that about half of drugs acting on mammalian cells in the market act through membrane proteins.

Recent advances in experimental structural biology, specially over the last decade, have accumulated a wealth of structural information on membrane proteins, revealing key elements for their function. However, it became soon evident that static structures are not sufficient to fully characterize the function of membrane proteins, and that in order to fully understand their mechanism, a dynamical description of membrane proteins is necessary. Conformational and interaction dynamics exert a dominant influence on the functional behavior of membrane proteins, for it is the interplay between structure and dynamics that ultimately defines a biological system's functional mechanism. Knowledge of how these fundamental phenomena influence the way membrane proteins function will be required to understand both the complex web of signaling and energy transduction mechanisms required for normal cellular function and their pathologies.

Having a long tradition in studying a wide range of membrane proteins in collaboration with leading experimental groups in the world, it was very natural for the Resource to join efforts with a stellar group of researchers with the common goal of applying state of the art biophysical methodologies to investigate at an unprecedented level the structural dynamics of membrane proteins. As a result of this joint effort, the "Membrane Protein Structural Dynamics Consortium (MPSDC)" was formed and recently (May 2010) was funded through a "Glue Grant" by the NIH National Institute of General Medical Sciences. the consortium aims at addressing fundamental dynamical phenomena in membrane proteins through a highly interactive, tightly integrated and multidisciplinary effort focused on elucidating the relationship between structure, dynamics and function

in a variety of membrane proteins. The MPSDC is organized around multidisciplinary project teams formed by investigators from 14 institutions in five different countries. These teams will study major mechanistic questions associated with membrane protein function as it relates to two major areas: energy transduction in signaling (ion channels and receptors) and energy inter-conversion (transporters and pumps). Ultimately, our goal is to decode the general mechanistic principles that govern protein movement and its associated fluctuation dynamics by dissecting and analyzing the molecular and dynamical bases of these functions at an unprecedented and quantitative level, as well as exploiting this information to engineer altered and novel activities into membrane protein frameworks to rationally evolve new functions.

To accomplish its goals, the MPSDC will develop in parallel a set of tools, concepts and reagents to: (1) apply state of the art spectroscopic methods (e.g., magnetic resonance, fluorescence, 2D-IR) to follow conformational changes and dynamics of the determined structures; (2) correlate dynamic measurements with high-resolution ensembles and single molecule functional measurements; and (3) design and implement novel computational approaches to link static and dynamic data with function. Core facilities will feed and interconnect with the individual projects in a highly interactive way. The cores will act as both, "innovation incubators" and research support centers by providing service and expertise in these critical areas: membrane protein expression, the establishment of chemical synthesis capabilities for probes and detergents, the generation of a variety of binders and other crystallization chaperones and other target binders, and the development of common computational tools to interpret and integrate the wealth of experimental data. The Resource participates in the computational core through development of methodologies and tools that are required to integrate experimental data into computational models, and to describe large-scale motions of membrane proteins. The researchers of the Resource are also directly involved in a number of "bridging" and "pilot" projects investigating the mechanism of specific membrane proteins. Through this highly collaborative effort between leading experimental and computational groups in the areas of membrane proteins, the MPSDC will bring a dynamical view to our understanding of function of this important class of biological molecules.

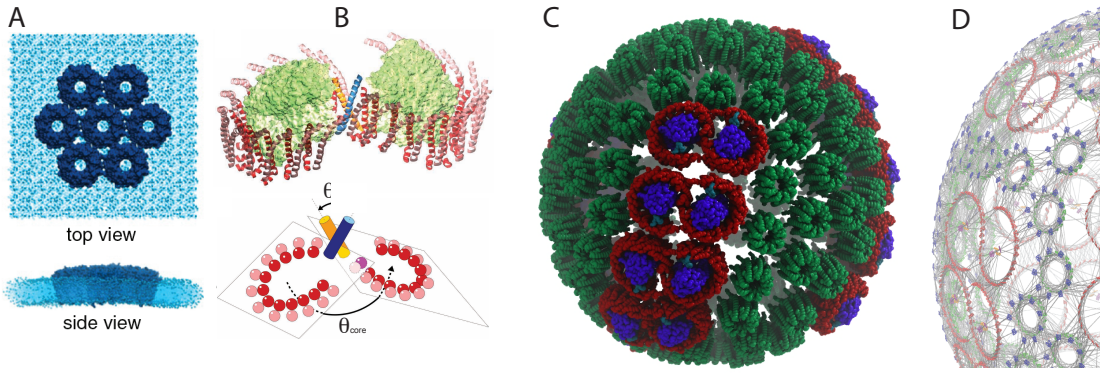

Figure 5: Protein complexes LH2 (A) and LH1-RC (B) constitute the bulk of a chromatophore vesicle. Inter-protection interactions between these complexes is responsible not only for the shape of the chromatophore [23, 27] but also for the separation of its constituents into domains between which quinone diffusion takes place. The all-atom chromatophore model that will be simulated is shown in (C). This structural model combines AFM data [28] with spectral studies [29] to more accurately account for the stoichiometry of constituent proteins [20, 25] The network of proteins and the constituent pigments (D) enable the computation energy transfer pathways in a chromatophore [20, 25, 26].

Lightharvesting in purple bacteria

Most life on earth is sustained by solar energy harvested by photosynthetic organisms. The simplest such organisms are purple photosynthetic bacteria that fuel their energy needs by producing one of nature's oldest and simplest photosynthetic systems. The bacterial photosynthetic unit, a pseudo-organelle called chromatophore, consists of several hundred proteins, but only a few different protein types. The bulk of the photosynthetic unit consists of light-harvesting complexes I and II (LH1 and LH2) and reaction centers (RC). Chromatophores are formed by different bacterial species into distinctive shapes, the most common being flat lamellar folds or spherical vesicles [17–19]. Each chromatophore organizes its constituent proteins into a fully functional photosynthetic unit. Recent work done by the Resource[‡] had focused on the determination of an all-atom chromatophore structure based on AFM data [20], on the structure and mechanism of individual proteins [21], on the effects of subassemblies of proteins on chromatophore curvature [15, 16, 22, 23], and on the excitonic network formed by the light-harvesting complexes to bring about efficient flow of energy to the RCs [15, 20, 24–26]. The structure and function of chromatophores is relevant by association also to the study of membrane morphonegensis and cellular energy production.

During the last funding period, the Resource has developed multiple structural and functional models for light harvesting in purple bacteria. A LH1-RC-dimer model was developed with Resource collaborators via the molecular dynamics flexible fitting method [16].

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

The location of PufX in the LH1-RC-PufX dimer was studied using the free energy perturbation method as implemented in NAMD [21]. The shaping of membrane curvature by LH1-RC dimers has been studied by MD simulations [16,21,22,27]. Curvature induced by LH2 and LH2-LH1-monomer aggregates, similar to those found in native chromatophores, was also studied [23, 27].

Structural studies of LH2 and LH1-RC complexes along with their effects on membrane curvature have allowed Resource scientists to develop models for the formation and photosynthetic function of chromatophore vesicles. Additionally, Resource scientists developed computationally demanding dissipative quantum dynamics methods to describe the dynamics of excitation energy transfer within and in-between light harvesting complexes [26, 30]. Working with Resource collaborators, it was found that the excitation energy transfer properties of a spherical chromatophore place constraints on the packing density of light harvesting proteins [25, 30]. These constraints also provide insight on the diffusion of quinones as charge carriers from RCs. The resource is currently developing a 20-million-atom LH1/LH2 system as well as an atomic-scale model of a complete spherical chromatophore which when solvated contains approximately 100 million atoms. This first study of a functional cellular unit at atomic scale will provide insight to how efficient light harvesting is achieved in nature.

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Subprojects

BTA UNIT: T

TITLE: Petascale Biomolecular Simulation

KEYWORDS: molecular dynamics simulation, high-performance computing

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ABSTRACT: The Resource is preparing both software and hardware to utilize the NSF-funded IBM Blue Waters sustained petascale computing system to be installed on campus in 2011. A NAMD [1] simulation of 100 million atoms is specified as an acceptance test for the machine, resulting in unprecedented levels of assistance in preparing NAMD to run reliably and efficiently.

A new binary file format for efficiently storing and accessing 100-million-atom molecular structures has been implemented as a VMD molfile plugin. NAMD can read this format and compress the bonding structure by identifying common repeated structures, greatly reducing the static replicated data that is stored on every node. NAMD reads the remaining per-atom data using dedicated input/output threads scattered across the machine, which also write the trajectory output file. A new load balancer is similarly distributed and hierarchical.

The Resource has been competitively awarded one of the first Petascale Computing Resource Allocations, which will be used to explore four processes: protein elongation in the ribosome, structural transitions in poliovirus entry, sculpting cellular membranes by BAR domains, and energy conversion by the chromatophore organelle. These collaborative projects will stretch the capabilities of the Resource at every level.

In order to locally store, analyze, and visualize the massive data produced by petascale simulations, the Resource was competitively awarded an NIH small equipment grant to assemble a "Petascale Molecular Dynamics Data Processing System" with over 200 terabytes of storage, graphics-processor-accelerated compute servers, and a large-memory, ultra-high-resolution visualization system. VMD has been extended with a message-passing interface to allow user-written scripts to easily coordinate distributed analysis calculations in this environment.

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 [2] 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) [3] and X-ray crystallography [4]. 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 [4] 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.

Certain nascent proteins regulate ribosome function while they are still being synthesized. Many of these regulatory nascent proteins play an important role in the control of gene expression in both bacteria and eukaryotes. Resource scientists, jointly with the Beckmann lab, obtained an atomic model of the ribosome stalled by the regulatory nascent peptide TnaC [5]. The atomic model was obtained by applying the molecular dynamics flexible fitting (MDFF) method, developed by the Resource [6, 7], to a 5.8-Angstrom cryo-EM reconstruction of the E. coli ribosome stalled by TnaC. The model revealed the precise mechanism by which TnaC inhibits termination of protein synthesis by the ribosome. Reorientation of two critical ribosomal residues prevents binding of release factors, which are responsible for terminating protein synthesis when the ribosome reaches a stop codon [5]. In a follow-up work, Resource scientists employed a range of computational techniques, including extensive molecular dynamics simulations, quantum chemistry calculations, and bioinformatic analysis, to determine how TnaC is recognized by the ribosome [8]. Two critical TnaC residues, Trp12 and Asp16, are recognized by the ribosome via a cation-pi interaction and a salt bridge, respectively. Mutations of TnaC predicted to alleviate stalling were also proposed and tested computationally. The reported work allowed a large body of biochemical data to be interpreted under a structural framework and provided the basis for designing new experiments addressing regulation of the ribosome by nascent chains.

BTA UNIT: C

TITLE: The Protein-Conducting Channel

KEYWORDS: translocon, SecY, translocation, protein channel, ribosome

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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 [9]. However, being able to enhance recognition and passage across the membrane could increase yields for artificially created proteins such as insulin [10]. 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.

Studies of the translocon in the past year have focused on its interactions with the ribosome, which is itself a driving project of the structural systems biology core of the Resource. Experimental structural data on ribosome-channel complexes is limited to cryo-electron microscopy maps, which do not provide atomic resolution [11–15]. Resource investigators have circumvented this limitation by utilizing the Resource's molecular dynamics flexible fitting (MDFF) method [6, 7], allowing the fitting of individual components, ribosome and channel, to maps of complexes via MD simulations. This method was applied to three maps from Resource collaborators, that of an inactive bacterial ribosome-translocon complex [16], a mammalian ribosome-Sec61 complex [14], and most recently, an actively translocating ribosome-translocon-nascent-chain complex [15]. The resulting atomic-scale structures revealed similar patterns of binding between ribosome and channel; additionally, in all cases, the channel is monomeric. The resulting structures were also used to carry out simulations of the ribosome-translocon complex. In the inactive case, simulations of the full 2.7-million-atom system illustrated how ribosome binding can influence the channel, by loosening the plug, which helps maintain the channel's closed state [16, 17]. Simulations of the active ribosome-channel-nascent-chain complex, which took advantage of the GPU-accelerated version of NAMD [18, 19], further demonstrated unique ribosome-lipid interactions that may aid the proper orientation and insertion of the nascent chain's signal anchor into the translocon [15]. Future studies will focus on the process of signal-anchor insertion from ribosome to translocon, including other factors that govern its orientation.

BTA UNIT: C

TITLE: Your subproject title

KEYWORDS: Your subproject keywords

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% BTA $: BTA %

ABSTRACT: ABSTRACT including a URL to something in the first paragraph (http://www.ks.uiuc.edu/Rese

Introduce your system with cites [1] in the first paragraph. Say where it is found, what it does, and why it is interesting (mention available structure and what experimentalists are interested in most).

Briefly describe your work: how the structure was prepared, how many atoms it included, what the simulation conditions were. Be sure to mention NAMD in regard to MD simulations and VMD in regard to data analysis. Tell briefly what the most interesting findings were. List the published and submitted articles over the funding period.

BTA UNIT: C

TITLE: The Photosynthetic Chromatophore

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

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ABSTRACT: The chromatophore is a pseudo-organelle that is responsible for harvesting light and subsequent conversion of light energy to chemical energy in the form of ATP (http://www.ks.uiuc.edu/Research/psures). After initial excitation from photon absorption by the light harvesting proteins in the chromatophore, excitation energy is tranferred in a multi-step process to a reaction center (RC). At the RC the excitation energy is used to charge a quinone molecule, which then diffuses through the protein-rich chromatophore membrane to a bc_1. There the charged quinone is oxidized yo produce a proton gradient across the membrane, which in turn drives ATP production by ATP synthase. In purple bacteria, such as Rhodobacter sphaeroides, the protein responsible for photon capture are known as light harvesting complex 1 (LH1) and light harvesting complex 2 (LH2). LH1 associates with two other proteins found in the chromatophore, RC and PufX, to form LH1-RC-PufX dimer complexes. LH2 and LH1-RC-PufX have a dual function; not only are they responsible for capturing light energy, they also induce membrane curvature to shape the chromatophore into, e.g., vesicles or tubes. Therefore, the system is relevant to understand two fundamental questions in biophysics, namely membrane morphonegensis and cellular energy production.

Resource efforts to develop a comprehensive model of photosynthesis in chromatophores have addressed multiple structural and functional questions in the past year. The LH1-RC dimer model developed with Resource collaborators using molecular dynamics flexible fitting [20] was further built upon to investigate the location of the protein PufX in the LH1-RC-PufX dimer [21]. Utilizing the free energy perturbation method as implemented in NAMD, it was found that that PufX likely resides at the center of the LH1-RC-PufX dimer, where it can induce the previously

observed bending of the dimer [20–23]. Curvature induced by LH2 and LH2-LH1-monomer aggregates, similar to those found in native chromatophores, was also studied [23, 24]. It was observed that the interaction of bulky, charged residues on one side of LH2 are the primary curvature-inducing factor in LH2-only aggregates, while an LH2-LH1-monomer aggregate did not develop curvature, in agreement with experimental observations [24, 25]. Now, Resource scientists are constructing a larger system, requiring 20 million atoms, of LH1 and LH2 complexes in an experimentally observed arrangement [25]. To simulate this system, improvements to NAMD, including, e.g., the development of compressed structure and coordinate data formats, have already been made.

The crystal structure of LH2 and the modeled structure of the bent LH1-RC-dimer have allowed the study of the functional aspects of the chromatophore and its light harvesting components in unprecedented detail. Newly developed code by Resource scientists, implementing computationally demanding dissipative quantum dynamics methods, permits calculation of the dynamics of excitation energy transfer within and between light harvesting complexes [26]. This has elucidated the mechanisms of excitation transfer within and between LH2 complexes [26] and within LH1 complexes [27]. Working with Resource collaborators, it was found that the excitation energy transfer properties of a spherical chromatophore place strong constraints on the packing density of light harvesting proteins [28], whereas for a tubular chromatophore, the connection between energy transfer and packing density is much weaker [27]. This has provided insight for the ongoing investigation of how quinones can diffuse in the densely packed chromatophore membrane, which is an important question in the field of photosynthesis. In addition to the 20-million-atom LH1/LH2 system noted above, Resource scientists are also constructing an atomic-scale model of a complete spherical chromatophore consisting of all the component proteins required for photosynthesis, requiring 100 million atoms. The simulation of this system will represent a further breakthrough in the scale of systems currently being simulated using molecular dynamics and will provide important insights into the dynamical aspects of the chromatophore structure and function as a single photosynthetic unit.

BTA UNIT: C

TITLE: Molecular Modeling of Tamiflu Resistance For Influenza N1 Neuraminidases

KEYWORDS: swine flu, neuraminidase, oseltamivir, resistant

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ABSTRACT: ABSTRACT Oseltamivir (tamiflu) [29] is currently the main antiviral drug for treatment of H1N1pdm, more commonly known as "swine flu" (http://www.ks.uiuc.edu/Research/sw The drug functions by competitively inhibiting neuraminidase (specifically N1 subtype), a flu specific glycoprotein that is responsible for mediating the release of newly synthesized virions [30]. In effect, oseltamivir stems viral infection by preventing the virus from leaving an infected cell. Of great concern however, is the emergence of point mutation induced drug resistance to oseltamivir for H1N1pdm strains already reported in North America and Europe [31–33]. In order to develop new and effective therapies, it is therefore critical to understand both the specific interactions responsible for binding oseltamivir with influenza N1 subtype neuraminidases and the mechanisms responsible for mutation-induced drug resistance.

Previous computational studies regarding the mechanism for mutation-induced oseltamivir resistance in H5N1 avian influenza have suggested that the mutations

weaken drug binding by altering the hydrophobicity of the drug binding pocket [34, 35]. However, little is known about the actual drug binding pathway, or whether drug resistance may arise by preventing the drug from even accessing the binding pocket. In collaboration with the group of Thanh Truong (Unversity of Utah), the Resource is engaged in two investigations focusing on H1N1/H5N1, the first on drug interactions and the second on drug resistance.

Our first investigation involved a sequence analysis which showed that H1N1pdm neuraminidase shares a highest sequence identity with that of avian H5N1. Therefore, a molecular model of H1N1pdm neuraminidase, which has not been solved by experiment, was built by the Resource based on an H5N1 template (PDB entry 2HU4 [36]). Functionally, the oseltamivir binding site of H1N1pdm is virtually identical to that of H5N1, save for a mutation at Y374N for H1N1pdm. Molecular models for drug resistant neuraminidases were also modeled, chiefly involving the known H274Y and N294S mutations. Molecular dynamics simulations were then carried out on both wildtype and mutant models of H1N1pdm and H5N1 neuraminidase bound with oseltamivir, revealing that a conserved network of hydrogen bonds within the drug binding pocket is responsible for stabilizing the association between drug and flu protein [37]. In the case of the H274Y mutation, there was a slight destabilization of drug binding due to the loss of hydrophobic interaction with a pentyl group in neuraminidase's binding pocket. However, since both residues 274 and 294 do not lie within the actual drug binding site, our first study concluded that there must exist alternate mechanisms through which the mutations induce drug resistance.

Our second investigation probed the role that charge distribution, on the surface of neuriminidase, plays in drug binding. Employing a GPU-accelerated implementation of the multilevel summation method [38], Resource scientists calculated the electrostatic potential maps across simulation trajectories for wildtype and mutant H1N1pdm/H5N1 systems bound to oseltamivir. Combined with force-probe SMD and long timescale relaxation simulations, the electrostatic maps reveal a drug binding pathway for oseltamivir highlighted by a narrow row of negative surface charges. The drug resistant mutations map directly onto this drug binding pathway, suggesting that this may be one mechanism through which such mutations resist oseltamivir [39].

BTA UNIT: T

TITLE: Petascale molecular dynamics data processing

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ABSTRACT: Biomedically-relevant cell-scale processes take place in molecular assemblies made of millions to hundreds of millions of atoms. Atomistic molecular dynamics simulation of these structures provides insight into their functional mechanisms; such simulations are extremely demanding and require petascale computational resources. The datasets that result are so large that existing workstations are too limited – in physical memory, processing and visualization power, and mass storage – to efficiently handle them. Common visualization calculations, such as three-dimensional maps of electrostatic potential fields across a long trajectory, can take minutes using a standard desktop workstation. As a result, a researcher's interactive analysis of a large simulation result is interrupted and slowed so much as to be virtually impossible; the Petascale Molecular Dynamics Data Processing System (MDDPS) is designed to overcome the shortcomings of desktop computer workstations and provides the necessary hardware features to enable practical interactive analysis and visualization of challenging petascale datasets. The Petascale MDDPS is a cluster of tightly coupled computers that operate as a cohesive unit to provide high-performance data analysis capabilities required by petascale MD simulations. The system is composed of synergistic storage, analysis, and visualization nodes connected internally and to external resources by separate high-speed networks.

While both of the Resource's software packages, NAMD and VMD, are well-tuned to current computer hardware, harnessing the next-generation capabilities of the Petascale MDDPS hardware requires additional software development.

In the past year many improvements were made to GPU-accelerated analysis algorithms in VMD, extending them to support parallel execution on multi-GPU workstations increasing performance by up to a factor or 8 over a single GPU, and adding support for execution on GPU-accelerated clusters [40]. The GPU algorithms in VMD increase performance for computationally demanding tasks such as calculation of electrostatic fields [38, 41–43], as well as the computation and display of molecular orbitals for visualization of quantum chemistry simulations [44]. In order to help address the computational demands of analysis of petascale molecular dynamics simulations, VMD has recently been adapted to support execution on clusters and supercomputers using MPI, the standard parallel computing suite. The new MPI-enabled VMD provides several parallel algorithms that enable researchers to write parallel analysis scripts without having to learn MPI or otherwise become experts in parallel programming. The new MPI-based parallel scripting feature makes it easy to perform complex molecular dynamics trajectory analyses in much less time than was previously possible, through simple extensions to the existing scripting commands. New molecule file plugin interfaces and file formats have been developed to support simulations of biomolecular complexes containing over 10 million atoms, greatly increasing I/O efficiency when operating on very large structure files and simulation trajectories. The "psfgen", "solvate", and "cionize" structure building plugins for VMD have been updated to take advantage of these new molecule file plugins and have been tested on petascale-class 100 million atom biomolecular complexes.

BTA UNIT: T

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

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ABSTRACT: VMD [45] 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, it has been tuned to provide higher compuational and graphical performance. VMD 1.8.7, the most recent version, was released on August 1, 2009. In the past year, many improvements were made to GPU-accelerated algorithms in VMD, supporting parallel execution on multi-GPU workstations and increasing performance by up to a factor of 8 over a single GPU. The GPU algorithms in VMD increase performance for computationally demanding tasks such as calculation of electrostatic fields [38, 41–43], and computation and display of molecular orbitals for visualization of quantum chemistry simulations [44]. In order to help address the computational demands of analysis of petascale molecular dynamics simulations, VMD has recently been adapted to support execution on clusters and supercomputers using MPI. The new MPI-enabled builds of VMD provide several parallel reduction primitives that enable researchers to write parallel analysis scripts without having to learn MPI or otherwise become experts in parallel programming. New MPI-based parallel scripting features make it easy to perform complex molecular dynamics trajectory analyses in much less time than was previously possible, through simple extensions to the existing scripting commands. New molecule file plugin interfaces and file formats have been developed to support simulations of biomolecular complexes containing over 10 million atoms, greatly increasing I/O efficiency when operating on very large structure files and simulation trajectories. The "psfgen", "solvate", and "cionize" structure building plugins for VMD have been updated to take advantage of these new molecule file plugins and have been tested on petascale class 100 million atom biomolecular complexes. The latest version of the MultiSeq [46] plugin adds improved support for nucleic acid structures and improves performance over previous versions.

Over 27,000 users have registered for VMD 1.8.7 since it was released on August 1, 2009. Alpha test versions of VMD 1.8.8 have been made available over the past year in order to allow users to test new features and give feedback to the VMD

developers.

BTA UNIT: T

TITLE: Scalable Molecular Dynamics Software NAMD

KEYWORDS: molecular dynamics simulation, high-performance computing

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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, 47]. NAMD employs the prioritized message-driven execution capabilities of the Charm++/Converse parallel runtime system (http://charm.cs.uiuc.edu/), allowing excellent parallel scaling on both massively parallel supercomputers and commodity workstation clusters. NAMD is distributed free of charge to over 37,000 registered users as both source code and convenient precompiled binaries. 8,900 users have downloaded multiple releases. The 2005

NAMD reference paper [1] has been cited over 1000 times. NAMD 2.7b2 was released in November 2009 and has been downloaded by over 4,200 users, 700 of whom are NIH-funded.

NAMD 2.7b2 added support for the TIP4 four-point water model as well as refinements to the collective variable, free energy, and grid force methods introduced in NAMD 2.7b1. NAMD 2.7b3, to be released soon, will include an implementation of the local, momentum-conserving Lowe-Andersen thermostat and support for the Drude polarizability model being developed for the CHARMM force field. Support for the Drude force field in NAMD will allow our collaborators to complete tests needed to validate the force field in a timely manner. Currently in development for future NAMD releases are the Generalized Born implicit solvent model and QM/MM simulations linked to the OpenAtom code.

2.7b2 is the first NAMD release to support graphics processor acceleration based on the CUDA technology from NVIDIA [18,48], demonstrating a performance increase roughly equivalent to 12 CPU cores for each accelerator unit and running in parallel across nodes. 2.7b3 will provide increased CUDA performance through block-based pairlists that reduce the amount of time spent finding atoms within the cutoff distance. Upcoming developments will target the new NVIDIA Fermi architecture, the first with a shared cache, and will add compatibility with the alchemical free energy methods currently supported only in the CPU version.

The released NAMD 2.7b2 Linux binaries include direct support for high-performance InfiniBand networks via the OFED "ibverbs" library. Previous binaries supported only ethernet networks and users were required to build Charm++ and NAMD against a local MPI installation to use increasingly affordable and common InfiniBand hardware. The new version is both more convenient and higher performance. One remaining usability issue, the need to write scripts to launch the NAMD under the control of a queueing system, will be eliminated by new support in Charm++ for launching non-MPI binaries using the MPI launch program (mpirun or mpiexec) that is already supported on the machine.

NAMD 2.7b2 includes the option to use a compressed molecular structure file format that greatly reduces the per-process memory needed to run large molecular systems. This will combine in NAMD 2.7b3 with a new distributed hierarchical load balancer and distributed input and output to allow simulations such as the 100-million-atom benchmark simulation for the NSF Blue Waters petascale machine to be run on systems with limited memory per node. Distributed storage for reduced memory usage is also enabled for external potentials discretized on multiple, finite grids, as used in the molecular dynamics flexible fitting method.

BTA UNIT: C

TITLE: Computational Facility

KEYWORDS: parallel computing, visualization, network

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ABSTRACT: The Resource's computational facility provides the necessary computational resources utilized by Resource scientists. The facility offers Resource researchers and collaborators tools such as large local disk storage for their files and research data, various computational machines and clusters for simulation and data analysis, and advanced visualization workstations and projection facilities featuring 3D stereoscopic visualization and imaging.

This facility saw many improvements over the past year(http://www.ks.uiuc.edu/Development/C

The Resource has 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 NSF's Large Resource Allocations Committee has increased to 38 million service units compared to 30.3 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 has recently upgraded its 8-node graphics

processing (GPU) cluster with nVidia Tesla C1060 processing cards. This upgrade allows for greater computational capacity and bolsters the Resource's continuing efforts in developing GPU-accelerated versions of the NAMD [1] (http://www.ks.uiuc.edu/Researc and VMD [45] (http://www.ks.uiuc.edu/Research/vmd) packages. The Resource has begun building a faster GPU cluster that will leverage the new nVidia C2050 processing cards. These cards offer vastly improved computational capabilities over the previous generation C1060 processing cards. Support for the general software development and testing activities of the Resource has been improved with additional workstations and high resolution displays that complement the existing public graphical workstations. In an effort to improve the capability of the public workstations, the Resource will be upgrading the workstations with more memory, more processing cores, and improved graphics power. Additionally, the Resource has purchased 20 quad-core workstations with large memory and advanced graphics systems to improve computation and molecular graphics work.

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 32 core Sun X4640 server outfitted with 256 GB of Random Access Memory (RAM). This server is in addition to an existing server with the similar configuration that the Resource upgraded to 256 GB of memory. Plans are in place to purchase more of these systems to give Resource researchers and collaborators even more access to large memory computational machines. The Resource will also be purchasing a new workstation with upgraded memory, graphics, and computational power to improve its visualization facility. The visualization facility has been greatly improved with the recent addition of a new high resolution stereoscopic projector and screen. As of last year, the Resource had 160 TB of available data storage on its local network. This will be further increased with an additional Sun X4540 server boasting 48 2-TB hard drives capable of serving data directly to the entire network. Plans are in place to purchase more of these servers to further increase disk space for Resource researchers and collaborators. The Resource will also be upgrading its core servers, such as web and mail servers, over the next year.

The Resource has been busy preparing its computational facility for the upcoming petascale computing capabilities offered by the National Center for Supercomputing Applications' (NCSA) Blue Waters supercomputer, expected to be operational next year. A major push towards increased local disk storage, computational resources, and graphical visualization capabilities will be necessary to utilize the vastly improved resources Blue Waters will offer.

BTA UNIT: C

TITLE: Membrane sculpting by BAR domains

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

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ABSTRACT: Proteins from the BAR domain superfamily [49], 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 [50, 51] from low-curvature liposomes. BAR domains form banana-shaped homodimers bearing a high density of positively charged residues on the concave surface [52–54], which facilitates sculpting of negatively charged membranes. However, single BAR domains induce only local membrane curvature [55, 56], while recent cryo-EM reconstructions [51] reveal that sculpting of membrane tubes and vesicles is performed by many BAR domains arranged in lattice-like scaffolds.

Previously, we found that lattice arrangements of one particular type of BAR domains, N-BAR domains, which are optimal for producing high membrane curvature, are composed of protein rows separated by 5 nm, and the stability of the rows is maintained through electrostatic interactions between BAR domains [56, 57]. Despite extensive studies, it still remains unclear how membrane curvature is generated by lattices of BAR domains, and whether other types of BAR domains employ similar mechanism in maintaining protein lattices and forming membrane curvature.

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 atoms 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 to be done in concert, i.e., a multiscale approach.

In the past year, an all-atom simulation of a 2.3 million atom system covering 1 microsecond probed the dynamics of N-BAR domain lattice in atomic detail [58,59]. Membrane bending was found to be arised from scraffolding of the membrane by the concave surface of the proteins, rather than protein insertion into membrane, thus resolving a long-lasting scientific dispute. Inspired by previous results, models describing membrane sculpting by another particular type of BAR domains, F-BAR domains, have been developed by Resources scientists at different levels of resolution, employing shape-based coarse graining (SBCG) that resolves overall protein and membrane shapes, and all-atom molecular dynamics that resolves detailed molecular interactions. The multi-scale simulations sampled many BAR domain lattice types and elucidated how the membrane curvature generated depends on the lattice type. Bending of membrane by F-BAR domains was found to arise from electrostatic attraction of positively charged F-BAR domain surface and negatively charged lipid head group. A molecular mechanism for the cell-scale action of BAR domains is emerging from the computational studies.

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.

BTA UNIT: C

TITLE: Molecular Dynamics Simulations of Protein Folding

KEYWORDS: protein folding, lambda repressor, villin headpiece

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ABSTRACT: ABSTRACT

One of the most significant challenges in computational biology today deals with the protein folding problem: how the sequence of a protein specifies its folded structure (and thus, function). Effort 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, a timescale which until recently was unattainable through simulation. However, owing 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 villin headpiece sub-domain, the lambda repressor, and the Pin1 WW

domain. Complementary experimental 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 30,000-70,000 atoms, and must be 5-10 microseconds in duration to observe complete folding events [60]. The necessary simulation timescales was obtained by using the molecular dynamics program NAMD developed by the Resource [1], which has been optimized to deliver performance of 100 ns per day on the folding system [61].

A series of MD folding simulations was performed on villin headpiece including the wild-type protein and a fast-folding mutant. The wild-type protein folded to the native state reliably in 6 microseconds, revealing a common structural transition in the final stages of folding [62]. The fast folding mutant, in contrast, was observed to fold to native state quickly in some trajectories, but did not fold in others in 8 microseconds. Based on kinetic analysis, we were able to propose new experimental observables to more accurately monitor the folding process, as well as several mutations that should accelerate folding [62]. Subsequent analysis of the trajectories using principal component analysis and a non-metric multidimensional scaling method revealed structurally heterogeneous folding pathways [63]. In addition, we have performed unfolding simulations of the lambda-repressor under various temperatures and pressures. The results of these simulations indicated the stability of the native state strongly depends on temperature and pressure; the high-pressure denatured states contain considerable amount of secondary structure, in agreement with experimental hypothesis [64]. We have also performed two independent 10-microsecond folding simulations of the lambda-repressor, starting from fully extended configurations. The trajectory at low temperature (T=329 K) reached a stable intermediate state with more helical structure than the native state. The other trajectory performed, at higher temperature (T=359 K), formed non-native tertiary contact with proper secondary structure element. These two ongoing simulation are aimed to reach 15 microseconds which is the experimental folding time.

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: 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 [65]. 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) [65]. In addition to electrical signaling in nervous systems, Kv channels play an important

role in the regulation of cardiac excitability and insulin release. In humans, malfunction of these channels can result in neurological or cardiovascular diseases such as long QT syndrome or episodic ataxia [66].

In collaboration with the Yarov-Yarovoy and Roux labs, the Resource has developed atomic models of the open and closed states of the Kv1.2 potassium channel [67]. The initial models of Pathak et al. [68] were refined through several stages of molecular dynamics (MD) simulation, using the program NAMD [1]. To validate the resulting models of Kv1.2, the gating charge that is transferred across the membrane upon activation of the channel was calculated from $\sim$1 microsecond of all-atom MD simulations of the two protein states. The contribution of individual charged residues of the channel to the total gating charge was also determined. Comparison of these individual contributions to the experimental values obtained for Kv channels [69, 70] indicated that the closed state model obtained in the simulations corresponds to an intermediate conformation of the channel observed previously in experiments [71]. Further refinement of the channel via steered molecular dynamics (SMD) simulations [72, 73] resulted in a final model for the closed state of the channel, in which the slight rearrangement of gating side chains (arginines) within the transmembrane field resulted in an additional charge transfer across the membrane. This additional charge transfer might correspond to a fast component in the gating transition of Kv channels identified in previous experiments [71].

BTA UNIT: C

TITLE: Multiscale Elasticity in the Muscle Protein Titin

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

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ABSTRACT: Titin is a mechanical protein

(`http://www.ks.uiuc.edu/Research/Categories/MechBio/`) that protects muscle from

overstretching by producing a restoring force when a muscle fiber is extended beyond its normal length. Defects in the titin gene have been correlated to muscular distrophy. Much of what is understood about titin today arose from single-molecule experiments [74–80] and computer simulations [81–86] which have shed light on how the structure of titin resist mechanical stretching forces.

Two separate studies were completed [87, 88]. The first study [87] addresses the timescale gap between experiment and simulation in the forced-unraveling event of a single titin domain. Restricted by available computational resources in the past, simulations employing the steered molecular dynamics (SMD) method typically were configured to unravel single titin domains within the nanosecond timescale, whereas the equivalent timescale in atomic force microscopy (AFM) experiments is on the order of millisecond. The difference in timescale poses the question if the molecular events observed in simulations are representative to those occurring in experiments. To address this issue, a set of simulations have been carried out

to systematically test the relationship between timescale and the unraveling events of a titin domain, with the longest simulation being in the microsecond range. The results of these simulations demonstrated that the same molecular mechanism governs the unraveling of a titin domain, and that measurements from simulations and experiments can be interpreted by a single mathematical model [87].

The second study [88], performed with Resource collaborator O. Mayans (Univ. Liverpool, UK), investigated the intrinsic elasticity of a chain of titin made of six connected domains (I65-70). The simulations measured two different modes of elasticity of titin, namely, the so-called tertiary and secondary structure elasticities. At low stretching forces, titin domains straighten out without unraveling, providing a soft elasticity (tertiary structure elasticity) that can be accurately captured by a statistical mechanical model. At higher stretching forces, titin domains unravel one by one, providing further elastic response (secondary structure elasticity) that matches also prior experimental reports.

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 [89].This regulation mechanism helps to explain why cells in the human body can carry identical DNA, but form completely different cell types. 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 [90, 91].

One of the Resource's collaborator, Gregory Timp, discriminated methylated DNA and non-methylated DNA using synthetic nanopores [92]. Another collaborator, Hermann E.Gaub, measured different forces needed to rupture methylated and

non-methylated DNA. Both experiments suggested that methylation changes the mechanical property of DNA. In the past year, to further understand the structural and dynamic properties of methylated DNA as well as developing new detection methods for DNA methylation, two atomic scale modeling experiments were carried out to complement two single molecule experiments: (i) resolving methylated and non-methylated C-G basepairs with synthetic nanopores and (ii) methylated and non-methylated dsDNA rupture measurements. In study (i), the Resource studied computationally how methylated and non-methylated C-G basepairs can be discriminated by dynamically stretching DNA in a synthetic nanopore by means of electric fields [92–95]. Simulations showed a difference in translocation speed between methylated and non-methylated DNA in a nanopore at 1 V bias. The simulations also revealed that the structure of DNA inside the nanopore is more ordered for methylated DNA than for non-methylated DNA [92]. In study (ii), extensive simulations of stretching and unzipping double strands of methylated and non-methylated DNA were carried out. The simulations showed that stronger force is needed to rupture two strands of methylated DNA than non-methylated DNA. Moreover, the simulations revealed an unusual zipper-like conformation of DNA. The analysis of rupturing DNA process suggested that interstrand base stacking stabilizes the unusual zipper-like conformation, and methylation enhances the base stacking of cytosine to its neighbors. Both sets of simulations demonstrated in atomic level detail the reasons for the differences in the mechanical properties of methylated and non-methylated DNA.

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 [96].

Only one X-ray crystal structure of lipid-free apo A-I has been determined [97]; 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 [98]. 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 [99]. The Resource utilizes these homogeneous and well-characterized nanodisc particles [100, 101] in molecular dynamics studies [102–107].

In order to study the assembly and structural transitions in nanodiscs and HDL, a coarse-grained molecular dynamics model was developed [103–109]. Prior simulations have focused on discerning the factors important in nanodisc self-assembly. Coarse-grained simulations starting from a randomized distribution of lipid, protein, and water were self-assembled into discoidal HDL particles. These simulations revealing that the particles initially assemble due to the hydrophobic interactions followed by tertiary structural rearrangement of the two protein strands to form a double-belt orientation surrounding a lipid bilayer [105, 107]. More recent simulations have focused on the maturation of the previously studied discoidal HDL into spherical HDL particles upon the absorption of cholesterol esters [110]. Coarse-grained simulations revealed that the HDL particles quickly absorb and partition the cholesterol ester molecules to the center of the particle forming a so-called hydrophobic core. The resulting mature spherical HDL was reverse coarse-grained [106] into an all-atom model and simulated. The 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.

BTA UNIT: C

TITLE: Developing Nanopores as Nanosensors

KEYWORDS: nanopore, DNA sequencing, genotyping, human genome, force spectroscopy, silicon, silica, ionic conduction, polymer nanopore, nanoprecipitation, 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 [111], but can also be artificially manufactured in silicon-based membranes [112] and polymer wafers [113]. 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. Prof. Timp proposed that, in the absence of cofactors, restriction 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 shown that there is a voltage threshold at which the enzyme EcoRI separates from the DNA-EcoRI complex [114]. In a second study, we have also shown that the threshold voltage depends on the DNA sequence at the recognition site and is independent of the pore geometry [115].

(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. It was shown that the voltage threshold depends on the diameter and the secondary structure of the DNA [116]. This discovery was further studied in a second joint-publication with Prof. Timp's group [117]. We found that for synthetic pores, the hpDNA can translocate via three modes: unzipping of the

double helix and in two distinct different distortions of the double helix. From simulations, we observed that the measured ionic current are related to different DNA conformations in the pore.

(iii) The Resource has been investigating the feasibility of sequencing DNA using a synthetic nanopore. MD simulations revealed that an alternating electric field produces a back-and-forth motion of DNA strands through a 1-nm diameter pore. As a result, the electrical recordings exhibit a sequence-specific hysteresis due to the tilting of DNA bases. Such hysteresis may produce detectable sequence-specific signals [118]. In another joint-publication with our experimental collaborators [119], we reviewed the prospects for DNA sequencing with synthetic nanopores, compared nanopore sequencing with available sequencing techniques, and elucidated the challenges to achieve single-base resolution.

(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 [120]. We also studied the dynamics of monovalent and divalent cations inside plastic polymeric nanopores, showing that divalent cations interact strongly with the polymer nanopore surface [121]. In another study [122], we showed that divalent cations adsorbed at the polymer surface are responsible for the formation of transient precipitates at the pore lumen. Such phenomena are known as nanoprecipitation and have been reported in experiments. Finally, we have revised the latest successes and current challenges of nanopore simulations in a recent publication [123].

BTA UNIT: T

TITLE: Quantum Chemistry Visualization in VMD

KEYWORDS: Quantum Chemistry, Molecular Orbitals, GPU Computing, Visualization

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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 an 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.

In the past year we have progressed from the prototype stage to production release of the GPU-accelerated molecular orbital calculation and rendering algorithms, enabling interactive animations of molecular orbitals within the most recent VMD

release [44]. Our innovation here is the ability to perform these calculations in just fractions of a second (compared to minutes using other tools). The single-GPU implementation achieves a factor of 100 speedup compared to the most efficient CPU implementation we have found to date. We have subsequently improved the performance level further with support for multi-GPU acceleration, yielding up to another factor of eight performance gain on 8-GPU workstations, giving a peak speedup of up to 800 versus a single CPU core. VMD is presently the only software tool we are aware of that incorporates this kind of GPU acceleration technique.

We have completed 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., it can be superimposed on standard structure data. Together, the GPU-based animation of quantum chemistry data and the existing framework will turn VMD into an unprecedented molecular visualization program.

BTA UNIT: T

TITLE: Acceleration of Molecular Modeling Applications with Graphics Processors

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

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ABSTRACT: Over the past several years, the hardware and software architecture of graphics processing units (GPUs) have evolved to the point that they can now be used for general purpose scientific computations. State-of-the-art graphics processors include hundreds of individual arithmetic units that can perform up to 2 trillion 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 algorithms for computation of three-dimensional electrostatic potential maps surrounding the biomolecules. These new GPU-accelerated algorithms, reported in [38, 42], yielded speedups of up to 26 or more relative to state-of-the-art CPUs. These algorithms have subsequently been incorporated into VMD, the molecular visualization and analysis package developed by the Resource [45].

GPU acceleration techniques have also recently been applied to NAMD, the parallel molecular dynamics package developed by the Resource. In molecular dynamics simulations, the majority of computation is typically focused on evaluation of forces between atoms that are not chemically bonded. As reported in [18, 19], the use of GPUs has been shown to accelerate this calculation by a factor of twelve over state-of-the-art CPUs, and can be deployed on GPU-accelerated computing clusters with good parallel scaling performance. GPU-accelerated NAMD runs have also been shown to improve power efficiency by a factor 2.7 times over conventional CPU-only clusters [40].

The Resource recently developed new algorithms to accelerate visualization of molecular orbitals through the use of GPU computing [44]. The implementation released in VMD 1.8.7 has achieved hundred-fold speedups over conventional CPU-based processing, enabling for the first time, the ability to compute molecular orbitals from wavefunction data on-the-fly at an interactive rate. Further performance increases have been enabled for workstations with multiple GPUs, enabling speedup factors as high as 412. This development promises to enable visualization of dynamics for quantum chemistry simulations, and will serve as the basis for visualization of other molecular properties.

BTA UNIT: T

TITLE: MultiSeq: Sequence and Structure Analysis Software

KEYWORDS: sequence, structure, software

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ABSTRACT: MultiSeq [46] (`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.

Over the past year the Resource has made several significant changes to the MultiSeq package. More of the MultiSeq components (RMSD and q) now work properly with both RNA and DNA. Numerous graphical changes were made to the interface

that provide the researcher with more useful information and feedback. One can now easily choose which of the MultiSeq data fields to view for each sequence in the main window, sequences with modified bases now have their (likely custom) 3-letter codes visible in the interface; many other minor interface changes serve to let the researcher more quickly find the information they are looking for as well as make fewer mistakes. A new version of the MultiSeq user's manual has been produced that more thoroughly covers the available MultiSeq options, and many bugs have been fixed throughout the MultiSeq package that affected robustness and ease of use.

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, including extending MultiSeq to use alternate alignment programs (such as MAFFT) in addition to the included program ClustalW.

BTA UNIT: T

TITLE: NAMD-Lite and Molecular Simulation Methods Development

KEYWORDS: molecular dynamics simulation, methods development

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

NAMD-Lite has assisted 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 [124,125]. GPU acceleration of the most computationally expensive parts of the multilevel summation method [38,42] and subsequent integration into VMD [45] (http://www.ks.uiuc.edu/Research/vmd/) have made it feasible to calculate electrostatic potential maps of the H1N1pdm virus across entire simulation trajectories to better understand how mutation H274Y causes resistance to the drug oseltamivir [39]. The reference implementation of the multilevel summation method in NAMD-Lite continues to be a source for improvements to the VMD implementation, including support for periodic boundary conditions and improvements in accuracy through the use of higher order interpolation. Related work is ongoing to further develop the multilevel summation method for the distributed memory parallelization necessary for its incorporation into NAMD [1] (http://www.ks.uiuc.edu/Research/namd/).

Over the past year, the Resource has finished implementing models for polarizable force fields. Accuracy of biomolecular simulation is improved beyond the conventional force field models that assign fixed partial charges to atoms by extending these models to include electron density response to an electric field. A polarizable force field based on classical Drude oscillators [126] being developed in part by collaborator Benoit Roux, U. Chicago, is now fully supported in NAMD and currently being employed by Roux and colleagues to finish developing the force field parameters. The force computation was initially prototyped in NAMD-Lite before its parallelization into NAMD. Novel to NAMD is the use of a dual-temperature Langevin thermostat for dynamical simulation of the Drude oscillators, providing more efficient parallel scaling than methods based on the Nosé–Hoover thermostat [127]. An alternative model for electronic polarizability using fluctuating charges [128,129] has also been implemented into NAMD, in collaboration with Charles Brooks' NIH Research Resource Center for Multiscale Modeling Tools in Structural Biology.

The Resource has also recently implemented McCammon's accelerated molecular dynamics method [130] that adds a bias potential to the true potential to enhance

the transition between potential energy wells in order to more efficiently sample the conformational space. The method was initially prototyped in NAMD-Lite before its implementation in NAMD.

BTA UNIT: C

TITLE: MDFF Development

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

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ABSTRACT: 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) [6,7], 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 [131].

New tools have been developed to aid the validation and correction of atomic structures during molecular modelling. The Chirality VMD plugin and the Cispeptide VMD plugin assist researchers to identify, visualize and fix chirality and cispeptide errors, respectively, and generate restraints to prevent such kinds of errors during MD simulations and MDFF. The SSrestraints VMD plugin automates the generation of secondary structure restraints required by MDFF. This plugin has been improved to include the generation of hydrogen bond restraints. A new feature has been developed to incorporate symmetry information of bio-molecules into MDFF to improve the quality of fitting. A test set, consisting of different types of bio-molecules in different conformational states, was created. The test set was used to systematically explore and optimize MDFF parameters for different types of bio-molecules and conformational changes.

BTA UNIT: C

TITLE: Timeline: Trajectory Analysis and Event Identification in VMD

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

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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 assess a static whole-trajectory plot remains the same.

The Timeline plugin (http://www.ks.uiuc.edu/Research/vmd/plugins/timeline/) for VMD [45] provides a whole-trajectory 2D raster plot of calculated properties: the time dimension is displayed horizontally, the structure-component dimension is displayed vertically, and the property of interest (e.g. RMSD, solvent-accessible area, secondary structure) is indicated by colored tiles. The calculations may be performed from among a set of built-in analysis methods or through user-defined algorithms. The zoomable 2D plot is interactively connected to the 3D molecular structure displayed in VMD: moving the cursor through a transition event apparent in the 2D view will show the corresponding structures, time steps, and motions

in the 3D view. A major update to the Timeline plugin was included in the August 2009 release of VMD 1.8.7.

Over the past year, since the VMD 1.8.7 release, the Resource has made several valuable additions to Timeline. Performance increases make Timeline practical to use with with very large structures. Timeline now has the ability to display pre-computed analysis results from a long trajectory while loading only a portion of the corresponding, data-intensive coordinate data set. There are also new built-in analysis methods, improvements to the data file format, and simplified batch computation for user-defined methods. We have also made user-interface enhancements – including expanded display of selection details, auto-scaling, and new color scale features – that enable users to explore analysis results more efficiently. In the coming year, the Resource plans to add features to Timeline that improve data management and analysis performance: multiple-trajectory and multiple-data set calculation and display, an interface for remote job spawning, and high-performance GPU-based calculation of common Timeline analyses.

Resource Summary

BTA unit: (T)

NUMBER PUBLISHED -

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

NUMBER IN PRESS -

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

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NUMBER IN PRESS -

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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

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

NUMBER IN PRESS -

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

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The Resource Advisory Board met September 20-21, 2009, at the home of the Resource for Macromolecular Modeling and Bioinformatics. Previously the Advisory Board had met in July 2008. The September 2009 Advisory Board membership and report is provided below.

Advisory Board Membership:

- Dr. Dave Thirumalai, Professor, College of Computer, Mathematical and Physical Sciences, Institute for Physical Science and Technology, University of Maryland at College Park (Chair)
- 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. Michael Heath, Director of Computational Science and Engineering, University of Illinois at Urbana-Champaign
- Dr. Olga Brazhnik, Program Officer, National Institutes of Health, National Center for Research Resources

Advisory Board Report, September, 2009 NIH Resource for Macromolecular Modeling and Bioinformatics

Introduction

The Advisory Board of the NIH Resource for Macromolecular Modeling and Bioinformatics (hereafter denoted the *Resource*) met on September 21, 2009. This is the second year of the current funding period (2008-2012), which makes it an important one as the unit positions itself for renewal in approximately two years. The present Advisory Board, which was assembled at the very beginning of the funding cycle, took this opportunity to discuss broad directions being pursued. It may be profitable for the participating faculty associated with the *Resource* to consider the recommendations of the Advisory Board as they prepare themselves for renewal.

The Committee was very impressed with Professor Klaus Schulten (Principal Investigator), the other faculty and staff associated the *Resource*, and their students. They are

doing outstanding science with impressive list of publications. Collectively their impact on the scientific community has been nothing short of spectacular. The science and the natural collaborations that they have established continue to be the engine that drives the entire *Resource*. The scientific collaborations, involving a variety of scientists both within the University of Illinois at Urbana-Champaign (UIUC) and worldwide, leads to questions that often require fundamental technological developments in the Nanoscale Molecular Dynamics (NAMD) software and hardware. In response to these needs the *Resource* has developed new algorithms (software) and has actively pursued the use of GPUs in speeding up the computations. These developments in turn continue to benefit the users whose number is continuously growing. Thus, the interplay between scientific inquiry and technology development has set the tone for the way the *Resource* operates, which has made this a very unique research center.

A real problem, apparently a burden of success, is that the popularity of the computer programs NAMD and Visual Molecular Dynamics (VMD) has greatly increased the number of users. The *Resource* does a remarkable job of supporting the users and helping them solve many of their problems. A natural result of this growth is that the ability of the software team to respond to users is compromised by the growing size of the community. This issue was already transparent during the Advisory Committee held in 2008. We think that, certainly in the long run, there is a need to add additional programmers to cope with the increasing demand from users. Given that the service provided by the *Resource* is unique it is felt that they should address this issue and perhaps implement the recommendation given last year.

All the core programs are contributing substantially to the current success of the *Resource*. However, they also need to sustain the long-term viability of the *Resource*. Hence, it may be necessary for the PI and others involved to re-align the cores so that the fundamental goals of the *Resource* are not compromised. We recommend that the PI should have the discretion to evaluate the missions of each of the core programs and make necessary changes either in response to developments in technology or science. Such realignment might involve phasing out certain aspects of the core programs and adding new ones. The Committee feels that these decisions should be at the discretion of the PI.

Accomplishments on all fronts (science, technology development, and the dissemination of service to the community) during the upcoming year are vital, as they will set the stage for renewal prospects. Coordination between the PI and the other faculty members is important so that not only outstanding science is done but also other tasks, that may appear peripheral to the scientific goals, are also completed.

Further details, organized by the research and development cores of the *Resource*, and a summary follow.

Collaborations

In addition to its own internal research and its development of methods, tools, and software for distribution to a broad research community, the *Resource* is engaged in a remarkable number of external collaborations that are extremely impressive in their diversity of research topics and their international scope. Many of these collaborations are with experimental groups and feature a close interaction between experimental and computational techniques, thereby providing a strong dose of realism to the modeling and simulation effort while also affording many opportunities for experimental validation of simulation results.

An excellent example of the close interplay between computations and experiments is molecular dynamics flexible fitting (MDFF), a new method developed by the *Resource* in which atomic structures are fit into cryo-electron microscopy (EM) maps using MD simulations with NAMD. The method consists of adding external forces proportional to the gradient of the EM map into an MD simulation of the atomic structure, while the stereochemical quality of the structure is preserved by the MD force field. This example also illustrates how such collaborations drive software development, in that the eternal forces from EM are defined on a grid, motivating the GridForces capability recently incorporated into NAMD. Other similar success stories have resulted from collaborations on steered molecular dynamics, the study of membrane proteins, and the effect of methylation on the mechanical stability of DNA. Additional collaborations have demonstrated the agility of the *Resource* in tackling timely problems, such as analyzing the H1N1 flu virus.

Such collaborations are a vital part of the mission of the *Resource*, as the challenges they pose drive model development and software robustness. The *Resource* has commendably focused on high quality collaborations with a wide variety of leading researchers on projects having significant impact and leading to a substantial number of publications. Collaborative projects are chosen both for their potential scientific payoff and to challenge the tools and software. Some caution should be exercised to avoid spreading *Resource* researchers too thinly, but thus far the benefits of the collaborations appear to be well worth the time and effort that has gone into them.

Bionanotechnology Core

Software development in the Bionanotechnology Core was driven by several experimental collaborations pursuing applications of inorganic nanostructures in nanobiotechnology. The *Resource* continued to develop grid-based approaches to simulations of biomolecules, which have already had many successful applications, for example the MDFF method. As a new development, the *Resource* has implemented and released a new version of the grid-forces code that allows an arbitrary number of grids to be used in an MD simulation.

In general, the Biotechnology Core combines biomolecular systems with solid-state and polymers systems that could form part of devices used for sequencing or detection. The

research involves the interactions of biomolecules (proteins and DNA) with four kinds of nanopores: polymer based, biomolecular, silicon and MOS. The most exciting collaboration of the Biotechnology core of the *Resource*, with G. Timp (UIUC), involves the prospects of using silicon nitride pores to detect methylation of dsDNA and DNA sequencing. The simulations of methylated DNA transport through a silicon nitride nanopore revealed that the voltage threshold for translocation critically depends on DNA methylation—a property that can be used for detection. Results presented to the Advisory Board showed how the development of 3D PMF potentials can be used to enhance the sampling and reduce the voltage noise such that different base pairs can be recognized. Using this method, the *Resource* researchers were able to extend the effective range of the simulations to the hundreds of microseconds, demonstrating that sequencing dsDNA is indeed possible.

Other collaborations include the study of ion conductance through silica nanopores determined the influence of the nanopore surface on the ion-voltage (I-V) dependence. *Resource* researchers have shown that adhesion of ions to the surface of a nanopore can dramatically alter its I-V curve, making it asymmetric. This research component did not involve the development of new technologies. Instead, a plug in into VMD was created to build the systems. Other scientific developments include the interaction of proteins with nanopores.

Structural Systems Biology Core

In the Structural Systems Biology Core, the *Resource* is carrying out cell-scale modeling techniques and the most highly visible collaborations are benefitting from the tools in the VMD visualization program. Major methodological developments were accomplished and incorporated into large scale simulations.

The Molecular Dynamics Flexible Fitting (MDFF) technique that was developed at the *Resource* has been used for simulation of several states of the ribosome, the bacterial flagellum, viruses and the translocon. It's through these highly demanding and very visible applications that the resource is pushing the tool development forward. The *Resource* has been exemplary in number of *Resource*-related publications of the five associated faculty in 2008 and 2009, namely 108. The citation numbers for Schulten papers (4,000) are astounding. The *Resource* is engaged 37 collaborative projects that involve mainly experimental laboratories. From these collaborations 53 joint publications resulted in 2008-2009. All collaborations fit extremely well the thrust and capabilities of the *Resource* since they embrace recent or new advances in computational technology, in theory, or in analysis methods. As required by these applications, the *Resource* is refining their tools to automate some of the steps, including building, simulation, and analysis of the results. An example of such refinement is the inclusion of secondary structure restraints.

Scientific breakthroughs were made through accelerated molecular dynamics method-

ology, such as combining single molecule experiments and modeling and on elucidating mechanical properties associated with function for the muscle protein titin. Coarse graining and GPU acceleration allowed studies of cell morphogenesis, electrostatics, and free energy calculations. Large scale molecular dynamics are still a "Schulten" best, such as investigations of the elongation intermediates of the ribosome, modeling of photosynthetic organelles in purple bacteria and whole cell modeling.

These structural cell biology applications are outstanding and an absolute necessary cornerstone in the success of the *Resource*.

Progress made by Emad Tajkhorshid and his group in simulations of membrane transporters has also been impressive. The simulations are carried out with great care and lend insight into the detailed molecular mechanisms underlying membrane transport.

VMD Core

Progress in VMD continues to be impressive, both in program development and in servicing an ever expanding user base.

Development in VMD follows two, somewhat different, directions. The first, led by John Stone, focuses on more traditional molecular graphics. The hard work devoted to incorporating graphics processing units (GPU) has been rewarded with greatly enhanced performance. Visualization of molecular orbitals from output of ab initio programs is especially impressive, and will greatly benefit both students and researchers. NAMD can also create input files for more specialized ray tracing programs such as POVRAY, so researchers are not limited. The trajectory analysis modules of VMD are very highly regarded.

While the primary use of this part of VMD is still Visualizing Molecular Dynamics, the tools can be applied a wide variety of data (e.g., MRI scans), and therefore can in principle enhance the creativity of many researchers. The *Resource* needs to make a conscious decision how far it wants to go with potential visualization everything and anything? The most serious challenge facing this effort stems from its success: user support requires an ever increasing proportion of the staff, making it difficult to devote efforts to program development. It will be difficult to solve this problem without additional staff, though other options should be considered. The implementation of user-forums, on-line tutorials, and search features has ameliorated some of the support burden. Can these efforts be further expanded? Ideally, staff should never have to provide information that is already available.

The second front, led by Zaida Luthey-Schulten, links sequence data with structure. It is somewhat open ended, at least partially because the links themselves are under development, or still need to be discovered. Hence, plug-in modules for standard sequence analysis programs, as well as new and highly innovative analysis tools developed by

Dr. Luthey-Schulten are included. Dr. Luthey-Schultens collaboration with Carl Woese is also adding exceptional value to the *Resource*. The Committee is impressed with both the broad idea of combining bioinformatics and atomic level descriptions, and the specific efforts presented. However, there exists a potential for loss of focus and conflict in development of VMD; e.g., could advances helpful for trajectory analysis and molecular graphics be compromised by the bioinformatics component?

Two suggestions:

1. Because this is the relatively newer part of the VMD package, special attention should be focused on setting up on-line documentation to avoid the huge support burden already described for the molecular graphics modules.

2. The *Resource* should consider recruiting an expert in Bioinformatics for the Advisory Board.

NAMD Core

NAMD is a highly parallel software tool to perform molecular dynamics of biomolecular systems. NAMD is the most advanced public domain code for performing simulations on large systems. The code has been distributed to over 16k users. The software takes advantage of a wide variety of computer architectures. The developers of NAMD have actively collaborated with national laboratories and industry (IBM) that have deployed new supercomputers such that the new versions of NAMD take advantage of the computers. The implementation of NAMD on different architectures and the distribution of resources are transparent to the user. Over the past few years new algorithms have been developed to perform non-bonding interactions. This algorithm is being implemented into NAMD versions that use GPUs. The porting of NAMD to GPU has been challenging since communication between GPU cores and the CPU are not optimal. NAMD gets a 10 fold acceleration with the use of GPUs.

The development of faster CPUs has been limited over the last few years. Instead, new computers use multiple cores and supercomputers that use 10^5 CPUS have become available. To take advantage of these architectures NAMD developers will concentrate in developing software that optimizes well on large systemsincluding million of atoms. The parallelization of smaller systems ($<$ 100,000 atoms) will be limited by communication bottlenecks.

The advisory board recognizes that NAMD must keep developing along as new architectures. There is a possibility that a new design of NAMD might be needed to improve its portability and robustness.

Service, Training, Dissemination, and Administration

The truly impressive aspect of the *Resource* is that despite a heavy load they carry in pushing the frontiers of science and computational technology forward they do a remarkable job of servicing the community. The service takes the form of well-organized and well-attended workshops where researchers are exposed to the tools needed for their research. Much of the service also can be found in an easy-to-navigate website which serves as a portal to the software, training material, and other resources. The efficacy of the *Resource* in technology transfer is most evident by the rapid and continuing growth in the number of users who access and use VMD and NAMD in their researches.

The hands-on training provided by the scientists in the *Resource* through training events and direct inquiries by e-mail is also worth mentioning. This component of the *Resource* is outstanding. The continuing pressure to provide excellent service will require additional human resources, if not now, but in the near future.

Summary

The driving force of the outstanding performance of the *Resource* continues to be the impressive accomplishments in science. The collaborations worldwide have given the *Resource* a panoramic view of the most outstanding problems in biology, which have in turn demanded integration of experimental and computational resources. The Advisory Board strongly concurs that the *Resource* is continuing its outstanding efforts to develop and distribute highly sophisticated modeling software and introduce these methods to a wide community. No significant adjustments to the research or service components are required.

The strongest recommendation of the Advisory Board is that the participating faculty members fully engage themselves in all activities of the *Resource* (Science, technology development, and service) so they can position themselves in about eighteen months for a successful renewal of this unique enterprise.

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 four research initiatives: biological intelligence, human-computer intelligent interaction, integrative imaging, and molecular and electronic nanostructures. Organizationally, the Resource belongs to the molecular and electronic nanostructures research initiative, where the emphasis is on developing a fundamental understanding of chemical and physical processes involving structures on the nanometer scale. The Resource is involved in close collaborative projects with other groups that are part of this research initiative, mainly in the area of biotechnology.

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

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

†`http://www.uiuc.edu/`

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

Internal Structures. Internally, the Resource is led by Principal Investigator (PI) Klaus Schulten, and Co-PIs Laxmikant Kalé, Zaida Luthey-Schulten, Emad Tajkhorshid, and Alek Aksimentiev with Dr. Schulten serving as Director. Guidance, information, and expertise is also provided by the Resource's Advisory Committee. Working under Resource leadership are three software developers, nine postdoctoral associates, 17 graduate students, three full-time 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 as 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, pro-

viding a valuable history of group decisions and issues. The office plan of the Resource, 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, further facilitates 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:

- 24,873 additional downloaders of VMD
- 6,318 additional downloaders of NAMD

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*`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/`

- 617 additional registered users of BioCoRE
- 4,548 VMD emails, 359 NAMD emails, and 179 BioCoRE chats and emails were exchanged in user support
- 4,273 citations of the VMD source paper; 1,892 citations of the NAMD source papers
- over 796,000 unique visitors to Resource software web site
- 15 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 155,586 users as of April 2010 (an increase of 24,873 or +19% since March 2009), with 35,975 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 1.8.7, has 27,002 downloading users since its release in August 2009, with 4,831 or 18% of downloaders indicating they are NIH funded users.

NAMD has been downloaded by 37,124 users (as of April 2010) (an increase of 6,318 or +20% since March 2009), of whom 8,807 or 24% are repeat downloaders. 6,475 (17%) of NAMD downloaders are NIH funded. The current version of NAMD, version 2.6 released in August 2006, has 16,284 downloading users, with 2,967 or (18%) of downloaders indicating NIH funding. The new NAMD beta, version 2.7b2, has 3809 downloading users since its release in November 2009.

BioCoRE has 4,268 registered users (an increase of 617, or +17% in the past year), involved in 585 projects (compared to 550 a year ago). A total of 222 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 2009-2010 include amongst other features:

- VMD has been adapted to run on HPC clusters, enabling much faster processing of complex simulation setup and analysis jobs using tens or hundreds of cluster nodes in parallel. User-developed analysis scripts can now be easily adapted for parallel execution on clusters.

- VMD makes 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. We have extended these capabilities further with support for dynamic load balancing of computations on multiple GPUs for even higher performance levels. The GPU accelerated features of VMD have also been adapted to work within cluster environments for parallel analysis runs on long-timescale simulation trajectories.

- VMD along with Tachyon now provides built-in support for sophisticated ambient occlusion lighting, for use in publication renderings and movie making. The movie making features of VMD have been extended with support for high-definition movie formats and support has been added for a wider range of movie compression tools.

- VMD includes the newly revised MultiSeq plugin version 3.0. Major efforts have been directed toward improving the ability of MultiSeq to handle large data sets, and the new MultiSeq is capable of loading and analyzing on the order of one hundred thousand sequences on a typical desktop machine. Additionally, MultiSeq can now correlate sequences and structures with other source of biological data, including the NCBI taxonomy databases, databases regarding microorganism growth temperatures, and enzyme function databases.

- VMD incorporates many improvements aimed at increasing its structure building capabilities. VMD reads, stores, and writes angles, dihedrals, impropers, and cross-term maps, and adds new text commands for querying these fields, enabling the development of flexible structure building tools such as the new topotools plugin. The latest version of the molefacture plugin adds the ability for users to build and use custom fragments. The new version also includes an interface for antechamber, providing users with autotyping and semiempirical geometry optimizations for fast

structure cleanup. Finally, a new graphical interface greatly simplifies the process of setting up free energy perturbation (FEP) calculations.

Scope of VMD User Support:

- 4,548 e-mail exchanges in response to user inquiries sent to the vmd@ks.uiuc.edu e-mail address
- 982 subscribers to the VMD-L mailing list, with 15,841 total postings, and 2,140 postings for the April 2009 - March 2010 period
- Local face-to-face support has been provided

There are currently 626 non-Resource users with access to the VMD source code repository, with 94 such users added in the last year.

Sites with Links to the VMD Site (via Yahoo! site search, April 2010): 4,243 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 2009-2010 include among other features:

- Support for the TIP4 water model
- Support for Drude polarizability model in CHARMM force field
- Local, momentum-conserving Lowe-Andersen thermostat
- Improved performance and feature set with GPU acceleration
- Direct (non-MPI) support for InfiniBand via OFED ibverbs library
- Distributed storage to reduce memory usage for grid-based forces
- Compressed molecular data format to reduce memory usage
- Distributed input and output
- Distributed hierarchical load balancer

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 NAMD Wiki user-editable web site contains 61 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"
- 828 subscribers to the NAMD-L mailing list, with 12,112 total postings, and 2,193 postings for the May 2009 - April 2010 period.
- Over 359 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 531 users with access to the NAMD source code repository, with 43 users added in the last year.

An automated nightly build system makes the latest NAMD source code, Linux x86_64, and Linux x86_64 CUDA binaries available for immediate download by users without repository access. These nightly builds were downloaded 6634 times by 2831 users in the 14 months since their introduction in March 2009.

Sites with Links to NAMD site (via Yahoo! site search, April 2010): 1,865 links

BioCoRE User Support:

- 23 emails issued to/from biocore@ks.uiuc.edu from April 2009 - March 2010
- 179 chat messages sent to the BioCoRE public help project from April 2009 - March 2010 within BioCoRE itself.

Sites with Links to BioCoRE site (via Yahoo! site search, April 2010): 266 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 2010 yielded 4,273 published journal articles, papers, or books citing the VMD origin paper [1]. Below are 25 recent citations:

- Giambasxu, George M. and Lee, Tai-Sung and Sosa, Carlos P. and Robertson, Michael P. and Scott, William G. and York, Darrin M. (2010). Identification of dynamical hinge points of the L1 ligase molecular switch. *RNA-A Publication of the RNA Society*, 16, 769-780.

- Limongelli, Vittorio and Bonomi, Massimiliano and Marinelli, Luciana and Luigi Gervasio, Francesco and Cavalli, Andrea and Novellino, Ettore and Parrinello, Michele. (2010). Molecular basis of cyclooxygenase enzymes (COXs) selective inhibition. *Proceedings of the National Academy of Sciences of the United States of America*, 107(12), 5411-5416.

- You, Hong and Zhang, Wenbao and Jones, Malcolm K. and Gobert, Geoffrey N. and Mulvenna, Jason and Rees, Glynn and Spanevello, Mark and Blair, David and Duke, Mary and Brehm, Klaus and McManus, Donald P. (2010). Cloning and Characterisation of Schistosoma japonicum Insulin Receptors. *PLoS ONE*, 5(3).

- Wang, Yong and Zocchi, Giovanni. (2010). Shape of Fair Weather Clouds. *Physical Review Letters*, 104(11).

- Liu, Feng and Maynard, Caroline and Scott, Gregory and Melnykov, Artem and Hall, Kathleen B. and Gruebele, Martin. (2010). A natural missing link between activated and downhill protein folding scenarios. *Physical Chemistry Chemical Physics*, 12(14), 3542-3549.

- Ganim, Ziad and Jones, Kevin C. and Tokmakoff, Andrei. (2010). Insulin dimer dissociation and unfolding revealed by amide I two-dimensional infrared spectroscopy. *Physical Chemistry Chemical Physics*, 12(14), 3579-3588.

- Kong, Ling-Ti and Denniston, Colin and Mueser, Martin H. (2010). The crucial role of chemical detail for slip-boundary conditions: molecular dynamics simulations of

linear oligomers between sliding aluminum surfaces. *Modelling and Simulation in Materials Science and Engineering*, 18(3).

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- Paruch, Robert and Rzeznik, Lukasz and Russo, Michael F. and Garrison, Barbara J. and Postawa, Zbigniew. (2010). Molecular Dynamics Study of the Effect of Surface Topography on Sputtering Induced by 20 keV Au-3 and C-60 Clusters. *Journal of Physical Chemistry C*, 114(12), 5532-5539.

- Jack, Rhonda and Sen, Dipanjan and Buehler, Markus J. (2010). Graphene Nanocutting Through Nanopatterned Vacancy Defects. *Journal of Computational and Theoretical Nanoscience*, 7(2), 354-359.

- Cubillos, M. and Sancy, M. and Pavez, J. and Vargas, E. and Urzua, R. and Henriquez-Roman, J. and Tribollet, B. and Zagal, J. H. and Paez, M. A. (2010). Influence of 8-aminoquinoline on the corrosion behaviour of copper in 0.1 M NaCl. *Electrochimica Acta*, 55(8), 2782-2792.

- Qiu, Hu and Ma, Shaojie and Shen, Rong and Guo, Wanlin. (2010). Dynamic and energetic mechanisms for the distinct permeation rate in AQP1 and AQP0. *Biochimica et Biophysica Acta- Biomembranes*, 1798(3), 318-326.

- Fotakis, C. and Gega, S. and Siapi, E. and Potamitis, C. and Viras, K. and Moutevelis-Minakakis, P. and Kokotos, C. G. and Durdagi, S. and Grdadolnik, S. Golic and Sartori, B. and Rappolt, M. and Mavromoustakos, T. (2010). Interactions at the bilayer interface and receptor site induced by the novel synthetic pyrrolidinone analog MMK3. *Biochimica et Biophysica Acta- Biomembranes*, 1798(3), 422-432.

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List of papers citing NAMD: A literature search in the ISI Web of Science citation database in April 2010 yielded 1,892 published journal articles, papers, or books citing the current [2] or prior [3] NAMD origin papers. Below are 25 recent cites:

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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 2009 - March 2010) the web site home pages for the Resources VMD[†], NAMD[‡], and BioCoRE[§] softwares showed substantial visitor traffic, as depicted in Table 1.

	Total	Month Avg.
VMD	236,752	19,729
NAMD	122,961	10,246
BioCoRE	18,602	1,550

Table 1: Application web site visits

Further Access

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

- *Visitor Program*
  The Resource visitor program invites members of the biomedical community to come to the Resource and get training on Resource software, as well as expert analysis of Resource members for scientific research problems of interest to the visitor. From May 2009 to April 2010, the Resource has hosted 12 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

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

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

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

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

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 196,000 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 2009-2010

Between May 2009 and April 2010 the Resource organized and hosted 15 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 23, 2010, Dr. Marcos Sotomayor, Harvard Medical School, Boston, MA, *Tip-Link Cadherins in Hearing and Deafness*
- Apr 19, 2010 , Professor Zoi Rapti, University of Illinois at Urbana-Champaign, Urbana, Illinois, *Coarse Grained DNA Models and how they can be used to Predict DNA Function*
- Apr 9, 2010, Dr. Hong Qian, University of Washington, Seattle, WA, *Cellular Signaling Dynamics and Computational Biochemical Systems*
- Mar 29, 2010, Professor Helmut Kirchhoff, Washington State University, Pullman, WA, *What Drives the Self-organization of Photosynthetic Membranes?*
- Mar 29, 2010, Professor Tracy Nixon, The Pennsylvania State University, University Park, PA, *Arginine-finger Dynamics Directs Rigid body Movement in the NtrC1 AAA+ ATPase, a Bacterial Enhancer Binding Protein that Regulates Transcription*
- Mar 8, 2010, Dr. Chen Zeng, George Washington University, Washington, DC, *Cell-Cycle Networks*

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

- Feb 15, 2010, Mr. Ali Hassanali, The Ohio State University, Columbus, OH, *Water at Molecular Interfaces: Structure and Dynamics near Biomolecules*
- Jan 25, 2010, Mr. Ivan Ufimtsev, Stanford University, Stanford, CA, *Electronic Structure of Proteins Solvated in Explicit Water: Insights from Ab Initio Molecular Dynamics Calculations on Graphical Processing Units (GPU)*
- Dec 7, 2009, Professor Peter C. Jordan, Brandeis University, Waltham, MA, *Normal Mode Studies of Conformational Change in Channels and Transporters*
- Dec 3, 2009, Professor Katy Borner, Indiana University , Bloomington, IN (slides), *Envisioning Biomedical Science*
- Nov 2, 2009 ,Professor Markus Deserno, Carnegie Mellon University, Pittsburgh, PA, *Coarse-grained Simulation Studies of Mesoscopic Membrane Phenomena*
- Sep 28, 2009, Dr. Arvi Freiberg, Tartu University, Estonia, *Squeezing Biomolecules*
- Aug 3, 2009, Dr. Jess A. Izaguirre, University of Notre Dame, Notre Dame, IN, *Simulation of Long Timescale Dynamics of Proteins Using Normal Mode Langevin Dynamics*
- Jun 17, 2009, Dr. Jerome Henin, University of Pennsylvania, Philadelphia, PA, *Cholesterol in the Nicotinic Acetylcholine Receptor*
- May 4, 2009, Dr. Adrian Elcock, University of Iowa, Iowa City, IA, *Molecular Simulations of Bacterial Cytoplasm*

Awards, Honors, and Special Recognitions

There are no items to list for the current year.

Dissemination

- 43 published articles and 11 in press in refereed journals or other publications
- Over 796,000 unique visitors to the Resource web site
- Over 17,400 article downloads from the Resource's publications database
- 603 reprint requests fulfilled by Resource staff
- 60 talks by Resource faculty and 29 presentations by other members
- 45 news stories about the Resource in various media outlets
- 38 requests to use Resource images or movies from external publishers or presenters
- Over 26,800 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 11 articles currently in press and 43 published articles by Resource members and collaborators published over the last year.

Articles In Press

- Jeffrey Comer and Aleksei Aksimentiev. Nanopore force spectroscopy: Insights from molecular dynamics simulations. *Nanopores: Sensing fundamental biological interactions at the single molecule level*. Eds. Rashid Bashir and Samir M. Iqbal., Springer, 2010. In press.
- Jeffrey Comer, David Wells, and Aleksei Aksimentiev. Modeling nanopores for sequencing DNA. Protocols in DNA nanotechology. Eds. Giampaolo Zuccheri and Bruno Samori. *Methods in Molecular Biology series*, Humana Press, 2010. In press.
- John Eargle and Zaida Luthey-Schulten. Simulation and visualization of dynamics in RNA:protein complexes.*RNA 3D Structure, Analysis, and Prediction*, eds. Leontis, N. and Westhof, E., 2010. In press.
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Published Articles

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- Rebecca Alexander, John Eargle, and Zaida Luthey-Schulten. Experimental and computational determination of tRNA dynamics. *FEBS Letters*, 584(2):376–386, 2010. [PMC in process]

- Fabien Archambault, Christophe Chipot, Ignacio Soteras, F. Javier Luque, Klaus Schulten, and Francois Dehez. Polarizable intermolecular potentials for water and benzene interacting with halide and metal ions. *Journal of Chemical Theory and Computation*, 5:3022–3031, 2009. [PMC in process]

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- 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*, 49:174–180, 2009. [PMC in process]

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- Ying Yin, Anton Arkhipov, and Klaus Schulten. Simulations of membrane tubulation by lattices of amphiphysin N-BAR domains. *Structure*, 17:882–892, 2009. [PMC in process]

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 796,000 unique visitors to the Resource web site, an average of 66,400 per month during the April 2009 – March 2010 period; visits during that period resulted

in 2.99 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.

	Total Visitors	Visitors per Month
VMD	236,752	19,729
NAMD	122,961	10,246
BioCoRE	18,602	1,550
Other Research	151,679	12,639
Galleries	26,143	2,178
Publications	41,175	3,431
Seminars	5,039	419

Table 2: Web site visitors from April 2009 - March 2010

A recent Yahoo! site search (April, 2010) found that 16,280 external sites link into areas of the Resource web site, with 1,095 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 by title, author(s), journal, subject, year ranges, and fulltext searching. Over 17,400 unique visitors downloaded at least one file copy of an article using the database over the April 2009 – March 2010 period. Additionally, 603 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 April 2009 - March 2010 period†:

Klaus Schulten

- April 2010, London England, Biological Interfaces: A TYC Computational Modelling Workshop, "New Synthesis of Experiment, Theory, and Simulation in the Crystallographic and Electron Microscopy Analysis of Ribosome Function"
- April 2010, MIT, Cambridge, MA, Greater Boston Area (Joint BU/Harvard/MIT) Theoretical Chemistry Lecture Series, "New Synthesis of Experiment, Theory, and

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

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

Simulation in the Crystallographic and Electron Microscopy Analysis of Ribosome Function"

- April 2010, Bad Herrenalb, Germany, First Principles Quantum Chemistry, 2010, "Quantum Biology of Animal Navigation - Or the Career Path Hans-Joachim Werner Did Not Take"
- April 2010, University of Illinois at Urbana-Champaign, TEDxUIUC, "The Computational Microscope"
- March 2010, Leiden, The Netherlands, Lorentz Center Workshop, "Entanglement and Spin-Dependent Reaction Channels in Radical Pair Processes"
- March 2010, Leiden, The Netherlands, Lorentz Center Workshop, "Quantum Measurement and Chemical Spin Dynamics", "Entanglement and Spin-Dependent Reaction Channels in Radical Pair Processes"
- February 2010, Zurich Switzerland, Prof. Dr. Viola Vogel, Department of Materials, Laboratory for Biologically Oriented Materials, "Molecular Mechanics of Muscle Elasticity"
- January 2010, Ventura, California, 5th Gordon Research Conference on Protein Folding Dynamics, "Microsecond Molecular Dynamics Simulations of Protein Folding - Successes, Failures, and Challenges"
- December 2009, Clearwater, FL, 3rd International Conference on Mechanics of Biomaterials & Tissues, "Molecular Mechanics of Muscle Elasticity"
- November 2009, Portland, OR, SC 2009, Computing for a Changing World, "Fighting Swine Flu through Computational Medicine"
- October 2009, Frankfurt, Germany, FIAS, Walter Greiner, Frankfurt Institute of Advanced Studies, University of Frankfurt, "Molecular Assembly and Teamwork - Bridge Between Inanimate and Animate Matter"
- October 2009, Heidelberg, Germany, Symposium at the Villa Bosch, Subcellular Microscopy and Probing, "Discovery of Subcellular Structures and Processes through the Computational Microscope"
- October 2009, University of Illinois at Urbana-Champaign, Illinois Imaging Workshop, "The Computational Microscope Images Biomolecular Machines and Nanodevices"

- September 2009, University of Illinois at Urbana-Champaign, Beckman Institute 20th Anniversary Symposium, Computational Biology of the Cell - The Next Decade, "Molecular Assembly and Teamwork - Bridge Between Inanimate and Animate Matter"

- September 2009, Berlin Germany, International Symposium on Protein-Cofactor Interactions of the Collaborative Research Center CRC-498, "Cryptochrome: Universal Magnetic Compass in Animal Navigation"

- July 2009, Blaine, WA, Foundations of Molecular Modeling and Simulation Conference, "Large-size, Long-time, Molecular Dynamics Simulations on a Budget"

- June 2009, Kyoto Japan, International Symposium on Reaction Dynamics of Many-Body Chemical Systems, "The Quantum Biology of Animal Magnetoreception"

- June 2009, London England, London Faraday Discussion, "Molecular Control of Ionic Conduction in Polymer Nanopores"

- June 2009, Manchester UK, University of Manchester, Manchester Interdisciplinary Biocentre, 2008/2009 MIB International Seminar Series, "The Computational Microscope"

- June 2009, Münster Germany, Molecular Cell Dynamics Symposium, "Single Molecule Experiments in Vitro and in Silico"

- May 2009, Berlin Germany, Molecular Kinetics 2009, "Common Structural Transitions in 50 Microseconds of explicit-solvent Simulations of Villin Headpiece Folding"

- May 2009, La Jolla, CA, Burnham Institute for Medical Research, "The Computational Microscope"

Laxmikant Kale

- November, 2009, Portland, OR, Doctoral Showcase, SC '09, "Automating Topology Aware Task Mapping for Large Supercomputers"

- October 2009, 2009 National HPC Workshop on Resilience, Arlington, VA, "Scalable Fault Tolerance Schemes Using Adaptive Runtime Support"

- August 2009, Urbana, IL, Scaling to Petascale Summer School, UIUC, "Load Balancing and Topology Aware Mapping for Petascale Machines"

- May 2009, New York, NY, International Conference on Supercomputing (ICS) 2009, "Dynamic Topology Aware Load Balancing Algorithms for MD Applications"

Zan Luthey-Schulten

- August 2009, UIUC Champaign, IL, Hands-on Computational Biophysics Workshop, "Evolution of Translation: Class-I Aminoacyl-tRNA Synthetases"
- August 2009, UIUC Champaign, IL, Hands-on Computational Biophysics Workshop, "Evolution of Translation: The Ribosome"
- August 2009, UIUC, Champaign, IL, Hands-on Computational Biophysics Workshop, "Evolution of Translation: EF-Tu:tRNA"
- July 2009, Santa Fe Institute, NM, NSF FIBR Teachers Workshop, "Evolution of Translation, "Class-I Aminoacyl-tRNA Synthetases"
- July 2009, Santa Fe Institute, NM, NSF FIBR Teachers Workshop,"Evolution of Translation: The Ribosome"
- July 2009, Santa Fe Institute, NM, NSF FIBR Teachers Workshop, "Evolution of Translation: EF-Tu:tRNA"
- July 2009, UIUC Champaign, IL, Hands-on Computational Biophysics Workshop, "Evolution of Translation: Class-I Aminoacyl-tRNA Synthetases"
- July 2009, UIUC Champaign, IL, Hands-on Computational Biophysics Workshop, "Evolution of Translation: The Ribosome"
- July 2009, UIUC Champaign, IL, Hands-on Computational Biophysics Workshop, "Evolution of Translation: EF-Tu:tRNA"

Emad Tajkorshid

- March 2010, San Diego, CA, University of California at San Diego, National Biomedical Computing Resource: "Dynamical View of Energy Coupling Mechanisms in Active Membrane Transporters"
- March 2010, St. Louis, MO, St. Louis University, Department of Biochemistry and Molecular Biology: "Dynamics of Membrane Binding and Activation of Coagulation Factors Captured at Atomic Resolution"
- February 2010, San Francisco, CA, Symposium at 54th Annual Meeting of the Biophysical Society: "A Dynamical View of Membrane Transporter Function at Sub-Angstrom Resolution"

- February 2010, Baton Rouge, LA, Louisiana State University, 17th Mardi Gras Conference 2010 on Computational Materials and Methods: "Visualizing the Art of Active Transport Across Cellular Membranes at Sub-Angstrom Resolution"
- February 2010, Baton Rouge, LA, Louisiana State University, 17th Mardi Gras Conference 2010 on Computational Materials and Methods: "Molecular Dynamics Simulation of Biomolecular Systems and Processes"
- October 2009, New York, NY, Weill Medical College of Cornell University, Department of Physiology and Biophysics, Institute for Computational Biomedicine: "Unraveling the Dynamical Basis of Membrane Transporter Function at Sub-Angstrom Resolution"
- September 2009, Urbana, IL, University of Illinois at Urbana-Champaign, Beckman Institute, Symposium on Computational Biology of the Cell - the Next Decade: "Simulating the Art of Active Transport Across the Cellular Membrane"
- September 2009, Tokyo, Japan, University of Tokyo, Intelligent Molecular Laboratory: "Computational Studies of Membrane Proteins and Processes at Different Size and Time Scales"
- September 2009, Tokyo, Japan, Riken Institute: "Visualizing the Dynamics of Membrane Transport at Sub-Angstrom Resolution"
- September 2009, Kyoto, Japan, International Symposium on Innovative Nanoscience of Supermolecular Motor Proteins Working in Biomembranes: "Coupling of Protein Conformational Transitions and Vectorial Substrate Translocation in Membrane Transporters"
- August 2009, Champaign, IL, iHotel and Conference Center, 'Hands-on' Workshop on Computational Biophysics: "Simulating Membrane Channels"
- August 2009, Champaign, IL, iHotel and Conference Center, 'Hands-on' Workshop on Computational Biophysics: "Parameters for Classical Force Fields"
- July 2009, Champaign, IL, iHotel and Conference Center, 'Hands-on' Workshop on Computational Biophysics: "Simulating Membrane Channels"
- July 2009, Champaign, IL, iHotel and Conference Center, 'Hands-on' Workshop on Computational Biophysics: "Parameters for Classical Force Fields"
- July 2009, Boston, MA, XXII Congress of the International Society on Thrombosis and Haemostasis: "Dynamical View of Membrane Binding and Complex Formation of Human Tissue Factor and Factor VIIa"

- June 2009, Bremen, Germany, University of Bremen, Summer School on Quantum and Classical Simulation of Biological Systems and Their Interaction with Technical Materials: "Molecular Dynamics Studies of Mechanisms of Permeation, Selectivity, and Gating in Membrane Channels"

- June 2009, Bremen, Germany, University of Bremen, Summer School on Quantum and Classical Simulation of Biological Systems and Their Interaction with Technical Materials: "Dynamical View of Energy Coupling Mechanisms in Active Membrane Transporters"

- May 2009, Cagliari, Italy, International Workshop on From Structure to Function: Influx and Efflux Systems :"Visualizing the Art of Active Transport Across Cellular Membranes at Sub-angstrom Resolution"

Aleksei Aksimentiev

- November 2009, Paris, France, French & American Young Engineering Scientists Symposium: "Molecular Modeling in Nanobiotechnology: The Case Study of a DNA Sequencing Device"

- November 2009, Seattle, WA, University of Washington, Department of Physics, Colloquium: "Physical Approaches to Sequencing DNA"

- October 2009, Urbana, IL, University of Illinois, Department of Physics, Colloquium: "Physical Approaches to Sequencing DNA"

- October 2009, Muncie, IN, Ball State University, Department of Physics, Colloquium: "Toward Sequencing DNA Using Nanopores"

- September 2009, University of Illinois at Urbana-Champaign, Beckman Institute 20th Anniversary Symposium, Computational Biology of the Cell - The Next Decade: "Molecular Modeling in Nanobiotechnology"

- June 2009, Bremen, Germany, 436th WE Heraeus Seminar: Biosensing with Channels: "Deciphering DNA Structure and Sequence from Ionic Current"

- April 2009, San Diego, CA, Advanced Sequencing Technology Development Meeting: "Molecular Dynamics Simulations of Nanopore Platforms for Sequencing DNA"

Other TCB members (includes meetings attended and poster sessions)

- April 2010, Urbana, IL, Department of Computer Science, 8th Annual Workshop on Charm++ and its Applications, "Charm++ Hits and Misses - A NAMD Perspective" (Jim Phillips)

- March 2010, Pittsburgh, PA, The 11th LCI International Conference on High-Performance Clustered Computing, Panel: "Pedal to the metal: Experiences programming accelerators for HPC" (Jim Phillips)
- February 2010, San Francisco, CA, 54th Annual Meeting of the Biophysical Society: "Single-Molecule and Molecular Dynamics Study of the Dimerization of Myosin Vi Medial Tail Domain" (Hyeong Jun Kim, Jen Hsin, Yanxin Liu, Monalisa Mukherjea, Daniel Safer, Anne Houdusse, H. Lee Sweeney, Klaus Schulten, Paul R. Selvin)
- February 2010, San Francisco, CA, 54th Annual Meeting of the Biophysical Society: "Steered Molecular Dynamics Simulation of Unfolding of Myosin Vi Proximal Tail Domain" (Yanxin Liu, Jen Hsin, Hyeong Jun Kim, Anne Houdusse, H. Lee Sweeney, Paul R. Selvin, Klaus Schulten)
- February 2010, San Francisco, CA, 54th Annual Meeting of the Biophysical Society: "The Role of MscS Cytoplasmic Domain as Osmolyte Filter" (Ramya Gamini, Marcos Sotomayor, Christophe Chipot, Klaus Schulten)
- February 2010, San Francisco, CA, 54th Annual Meeting of the Biophysical Society: "Recent Developments of the Molecular Dynamics Flexible Fitting Method" (Kwok Yan Chan)
- February 2010, San Francisco, CA, 54th Annual Meeting of the Biophysical Society: "Refinement and Validation of Atomic Models of the Kv1.2 Potassium Channel Through Molecular Dynamics and Gating Charge Calculation" (F. Khalili-Araghi, V. Jogini, V. Yarov-Yarovoy, E. Tajkhorshid, B. Roux, and K. Schulten)
- February 2010, San Francisco, CA, 54th Annual Meeting of the Biophysical Society: "The Role of the Protein-conducting Channel in the Membrane Insertion of Transmembrane Segments." (James Gumbart, Christophe Chipot, and Klaus Schulten)
- January 2010, Tokyo, Japan, Accelerated Computing (Riken/NVIDIA), "Accelerating Molecular Modeling Applications" (Jim Phillips)
- November 2009, Portland, OR, High Performance Computing with CUDA Case Study: Molecular Modeling Applications, CUDA Tutorial, Supercomputing 2009 (John Stone)
- November 2009, Portland, OR, Accelerating Molecular Modeling Applications with GPU Computing,Exhibition, Supercomputing 2009 (John Stone)
- November 2009, Portland, OR, OpenCL for Molecular Modeling Applications: Early Experiences, OpenCL BOF, Supercomputing 2009 (John Stone)

- October 2009, San Jose, CA, NVIDIA GPU Technology Conference, BOF Panel: "The Art of Performance Tuning for the CUDA Architecture" (Jim Phillips)
- October 2009, San Jose, CA, NVIDIA GPU Technology Conference: "Experience with NAMD on GPU-Accelerated Clusters" (Jim Phillips)
- October 2009, Urbana, IL, Beckman Institute Forum for Imaging and Visualization: "High Performance Molecular Visualization and Analysis with GPU Computing" (John Stone)
- October 2009, San Jose, CA, GPU Technology Conference: "GPU Accelerated Visualization and Analysis in VMD and Recent NAMD Developments" (John Stone)
- October 2009, Urbana, IL, UIUC, IACAT/CCOE GPU Brown Bag Forum , "An Introduction to OpenCL" (John Stone)
- September 2009, Urbana, IL, Beckman Institute for Advanced Science and Technology, Graduate Student Seminar Series: "Curvature-Inducing Properties of Light-Harvesting Complex II (LH2)" (Danielle Chandler)
- September 2009, New Orleans, LA, IEEE Cluster 2009, "High Performance Computing with CUDA: Biomolecular Modeling Applications of GPUs and GPU-Accelerated Clusters" (Jim Phillips)
- August 2009, Urbana, IL, Beckman Institute Graduate Student Seminar: Curvature-Inducing Properties of Light-Harvesting Complex II (Danielle Chandler)
- August 2009, Urbana, IL, NCSA, VSCSE: Many-Core Processors for Science and Engineering Applications, Multidisciplinary Panel (John Stone)
- August 2009, Urbana, IL, NCSA, VSCSE: Many-Core Processors for Science and Engineering Applications "Case Study - Accelerating Molecular Dynamics Experimentation" (John Stone)
- July 2009, Urbana, IL, NCSA, Careers in High-Performance Systems Mentoring Workshop: "Accelerating Molecular Dynamics on a GPU" (John Stone)
- June 2009, Philadelphia, PA, University of Pennsylvania, Center for Molecular Modeling: "GPU Accelerated Visualization and Analysis in VMD" (John Stone)
- May 2009, Waterloo, Ontario, Canada, University of Waterloo, Second Sharcnet Symposium on GPU and Cell Computing, Keynote: "Accelerating Molecular Modeling Applications with GPU Computing" (John Stone)

- April 2009, Urbana, IL, Beckman Institute for Advanced Science and Technology, Graduate Student Seminar Series: "Membrane Sculpting by BAR Domain Proteins" (Ying Yin)
- April 2009, Urbana, IL, Beckman Institute for Advanced Science and Technology, Graduate Student Seminar Series: "Molecular Dynamics Simulations of Villin Headpiece Folding" (Peter Freddolino)
- April 2009, Urbana, IL, NCSA, Path to Petascale: Adapting GEO/CHEM/ASTRO Applications for Accelerators and Accelerator Clusters: "Experiences with Multi-GPU Acceleration in VMD" (John Stone)
- April 2009, Urbana, IL, NCSA, Path to Petascale: Adapting GEO/CHEM/ASTRO Applications for Accelerators and Accelerator Clusters, "Experience with NAMD on GPU-accelerated clusters" (Jim Phillips)

Symposium - Computational Biology of the Cell - The Next Decade

On September 21-23, 2009, the Resource hosted a symposium titled "Computational Biology of the Cell - The Next Decade". The event brought together the best, most active, and most communicative scientists to discuss once-in-a-lifetime opportunities facing computational biologists, such as technologies in the form of petascale computers like Blue Waters, coarse-grained algorithms that permit explorations into entirely new scales of time and space, hybrid computational-experimental methods that will reveal cellular machines from the ribosome to the flagellum, and other topics.

Media Coverage

Stories involving the Resource appeared in popular media, online news sources, and other outlets during April 2009 – March 2010. The Resource recieved press interest for its research on how the ribosome interacts with other molecules to assemble new proteins and direct the proteins to a location in the cell[‡]. Resource research on the molecule *superoxide* and the role it plays in allowing birds to "see" the magnetic field of earth and use it for migration also drew press attention[§]. And, the Resource's use of the Ranger Supercomputer[¶] and GPU computing[‖] to combat the H1N1 swine flu virus were also subjects of media coverage.

[‡] http://news.illinois.edu/news/09/1123microscope.html

[§] http://news.illinois.edu/news/09/0622birds.html

[¶] http://www.statesman.com/business/content/business/stories/technology/\\06/04/0604Ranger.html

[‖] http://www.brightsideofnews.com/news/2009/11/19/researches-battle-h1n1-flu-virus-using-gpgpu-technology.aspx

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

- Greenemeier, L. (February 4, 2010). NSF teams with Microsoft to move scientific research into the cloud. *Scientific American (online).*
  `http://www.scientificamerican.com/article.cfm?id=nsf-microsoft-cloud`

- Staff. (January 15, 2010).

  Eyeing a growing market, Nvidia launches portal to aggregate GPU-enabled life science applications. *GenomeWeb Daily News.*
  `http://www.genomeweb.com/informatics/eyeing-growing-market-nvidia-\\launches-portal-aggregate-gpu-enabled-life-science-`

- Humber, A. (January 14, 2010). Tesla Bio Workbench enables scientists to achieve new breakthroughs. *NVIDIA Press Release.*
  `http://www.nvidia.com/object/io_1263450185923.html` *reprints*

  - Staff. (January 14, 2010). Tesla Bio Workbench enables scientists to achieve new breakthroughs in biosciences. *Marktewire.*
    `http://www.marketwire.com/press-release/Tesla-Bio-Workbench-Enables-Scientists-to-Achieve-New-Breakthroughs-in-Biosciences-NASDAQ-NVDA-1101727.htm`

  - Staff. (January 14, 2010). Tesla Bio Workbench enables scientists to achieve new breakthroughs in biosciences. *CNNMoney.com.*
    `http://money.cnn.com/news/newsfeeds/articles/marketwire/0576807.htm`

- Feldman, M. (January 14, 2010). NVIDIA takes aim at GPU acceleration for bioscience applications. *HPCWire.*
  `http://www.hpcwire.com/features/NVIDIA-Takes-Aim-at-GPU-Acceleration-for-Bioscience-Applications-81521012.html`

- Yates, D. (November 23, 2009). Computational microscope peers into the working ribosome. *UIUC News Bureau.*
  `http://news.illinois.edu/news/09/1123microscope.html`

  - Vieru, T. (November 29, 2009). Experts reveal the working ribosomes. *Softpedia.com.*
    `http://news.softpedia.com/news/Experts-Reveal-the-Working-Ribosomes-127838.shtml`

**`http://www.ks.uiuc.edu/Publications/stories.cgi`

  - Yates, D. (November 23, 2009). Computational microscope peers into the working ribosome. *EurekAlert!*. http://www.eurekalert.org/pub_releases/2009-11/uoia-cmp112309.php
  - Staff. (November 23, 2009). Computational microscope peers into the working ribosome. *NSF News From the Field*. http://www.nsf.gov/news/news_summ.jsp?cntn_id=116051&WT.mc_id=USNSF_195
  - Yates D. (November 24, 2009). Computational microscope peers into the working ribosome. *innovations report*. http://www.innovations-report.de/html/berichte/studien/computational_microscope_peers_working_ribosome_144214.html

- Valich, T. (November 19, 2009). Researchers battle H1N1 Flu virus using GPGPU technology. *Bright Side of the News*. http://www.brightsideofnews.com/news/2009/11/19/researches-battle-h1n1-flu-virus-using-gpgpu-technology.aspx

- Dubrow, A. (May 27, 2009). Inside the Swine Flu Virus. *TACC*. http://cms.tacc.utexas.edu/feature_stories/2009/inside_swine_flu.php

- Staff. (November 18, 2009). PRACE is ready for implementation: Applications ported. *HPCwire*. http://www.hpcwire.com/offthewire/PRACE-is-Ready-for-Implementation-Applications-Ported-70410637.html?ref=637

- Dublin, M. (October 22, 2009). GA Tech gets $12M for HPC development. *Genomeweb*. http://www.genomeweb.com/blog/gtech-gets-12m-hpc-development

- Wilson, S. (October 21, 2009). Georgia Tech wins NSF award for next-gen supercomputing. *EurekAlert!*. http://www.eurekalert.org/pub_releases/2009-10/giot-gtw102009.php

- Dublin, M. (October 1, 2009). Personal supercomputers? *Genome Technology*. http://www.genomeweb.com/informatics/personal-supercomputers

- Greenemeier, L. (September 30, 2009). Gaming tech aids scientists building virtual synthetic chromatophore. *Scientific American*. http://www.scientificamerican.com/article.cfm?id=gpu-aids-photosynthesis

- Humber, A. (September 28, 2009). NVIDIA collaborates with Microsoft on high performance GPU computing. *NVIDIA Press Release*. http://www.nvidia.com/object/io_1254126305481.html

  - Staff. (September 29, 2009). NVIDIA collaborates with Microsoft on high performance GPU computing. *PR Newswire*. http://www.prnewswire.com/news-releases/nvidia-collaborates-with-microsoft-on-high-performance-gpu-computing-62321757.html
  - Staff. (September 29, 2009). NVIDIA collaborates with Microsoft on high performance GPU computing. *TweakTown*. http://www.tweaktown.com/pressrelease/1964/nvidia_collaborates_with_microsoft_on_high_performance_gpu_computing/
  - Garner, D. W. (September 28, 2009). Microsoft, Nvidia team on GPU. *InformationWeek*. http://www.informationweek.com/news/hardware/data_centers/showArticle.jhtml?articleID=220300125

- Staff. (September 23, 2009). Understanding how birds navigate. *SPIE*. http://spie.org/x37204.xml?highlight=x2416&ArticleID=x37204

- Yates, D. (June 22, 2009). Toxic molecule may help birds "see" north and south. *University of Illinois News Bureau*. http://news.illinois.edu/news/09/0622birds.html *Reprints:*
  - Yates, D. (June 22, 2009). Toxic molecule may help birds "see" north and south. *Insciences Organization*. http://insciences.org/article.php?article_id=5820
  - Staff. (June 22, 2009). Toxic molecule may help birds "see" north and south. *e!Science News*. http://esciencenews.com/articles/2009/06/22/toxic.molecule.may.help.birds.see.north.and.south
  - Yates, D. (June 22, 2009). Toxic molecule may help birds "see" north and south. *EurekAlert!*. http://www.eurekalert.org/pub_releases/2009-06/uoia-tmm062209.php
  - Yates, D. (October 7, 2009). Toxic molecule may help birds "see" north and south. *MidwestAGnet*. http://www.midwestagnet.com/Global/story.asp?S=11273721
  - Staff. (Fall, 2009) Giftiges Molekül hilft Vögeln bei Orientierung (Toxic molecule helps birds navigate), Spektrum Augenheilkunde (2009, 23:299-303). http://resources.metapress.com/pdf-preview.axd?code=h765861217047384\&size=largest
  - Sandner, A.: (June 24, 2009) Zugvögel "sehen" das Erdmagnetfeld (Birds "see" the earth magnetic field): GEO.de. http://www.geo.de/GEO/natur/tiere/61087.html

  - Weitlaner, W. (June, 2009): Giftiges Molekül hilft Vögeln bei Orientierung (Toxic molecule helps birds to "see" north and south). Innovations Report. http://www.innovations-\-report.de/html/berichte/\\biowissenschaften_chemie/giftiges_molekuel_hilft_voegeln_\\orientierung_134708.html
  - Staff (June, 2009): Magnetsinn der Tiere entdeckt (Understanding how birds navigate). P.M. Magazin, http://www.pm-magazin.de/de/wissensnews/wn_id70.htm
  - Staff (June 25, 2009): Zugvögel: Gift-Molekül als Minikompass (Birds use toxic molecule as compass), scinexx, Das Wissensmagazin, http://www.g-o.de/wissen-aktuell-10095-2009-06-25.html

- Staff (October 30, 2009). Membrantransport von Proteinen (How proteins are being transported across membranes), *Internetchemie*

  http://www.internetchemie.info/news/2009/oct09/protein-membrantransport.html

- Staff (October 30, 2009) Licht am Ende des Molekularen Tunnels - Wie der Membrantransport von Proteinen durchgezogen wird (How proteins are being transported across membranes) *www.uni-protokolle.de* http://www.uni-protokolle.de/nachrichten/id/186993/

- Ganapati, P. (August 3, 2009). Personal supercomputers promise teraflops on your desk. *Wired*. http://www.wired.com/gadgetlab/2009/08/personal-supercomputers/

- Keim, B. (June 23, 2009). Reverse-engineering the quantum compass of birds. *Wired Science*. http://www.wired.com/wiredscience/2009/06/birdcompass/

- Ladendorf, K. (June 4, 2009). Ranger's new challenge: help fight swine flu. Supercomputer sibling Lonestar also wrangling with software to aid public health officials assess outbreaks. *Austin-American Statesman*. http://www.statesman.com/business/content/business/stories/technology/06/04/0604Ranger.html

- Dubrow, A. (May 27, 2009). Inside the swine flu virus. Researchers use Ranger supercomputer to discover how mutations in viral protein lead to drug resistance. *Texas Advanced Computing Center News*. http://www.tacc.utexas.edu/research/users/features/index.php?m_b_c=swineflu

- Minkoff, M. (May 20, 2009). Networks of computers analyze how networks of nerves in your brain talk to each other. *Medill Reports*. http://news.medill.northwestern.edu/chicago/news.aspx?id=130447

- Feldman, M. (May 4, 2009). NVIDIA shifts GPU clusters into second gear. *HPCWire*. http://www.hpcwire.com/features/NVIDIA-Shifts-GPU-Clusters-Into-Second-Gear-44324622.html?ref=622

- Jewett, B. (April 15, 2009). Closing the gaps. *NCSA News*. http://www.ncsa.illinois.edu/News/Stories/Gaps/

- 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 *Reprints*

  - Staff. (April 14, 2009). Researchers study signaling networks that set up genetic code. *EurekAlert!*. http://news.illinois.edu/news/09/0414pathways.html

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YouTube Movie Gallery

The Resource's gallery of movies[†] at the popular YouTube[‡] video hosting site continues to draw viewers. Established in October 2007, the site currently contains a library of 20 Resource videos, with seven new movies added during the period of April 2009 - March 2010. 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 be acknowledged when the movie is used, and that commercial use and derivative works are prohibited.

As of April 2010, the most viewed movies were "Water Channels in Cell Membranes"[¶] with 13,410 views, and "Lipoproteins that Circulate in the Blood Collecting Fat"[‖] with

[†] http://www.youtube.com/tcbguiuc

[‡] http://www.youtube.com

[§] http://creativecommons.org

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

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

11,942 views. The total count of all views of all listed videos since the gallery was started reached to around 55,844 views as of April 2010, representing 26,2810 views over the April 2009 - March 2010 period.

Training

The Resource has continued and expanded its training efforts through workshops, tutorial updates, case studies, hosting visitors, teaching classes, and graduate training. Whenever possible, training materials, tailored to support self-study, are made available via the Resource website for public consumption. 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 funding period include:

- Two week-long hands-on workshops on computational biophysics
- Nearly 76,000 views of all online tutorials
- Release of the *Molecular Dynamics Flexible Fitting* and *Structure Check* 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

Hands-on Workshops

Summer 2009 Workshops. In summer 2009 the Resource organized two hands-on workshops in computational biophysics, held at the iHotel and Conference Center in Champaign, Illinois, the hometown of the Resource. These five-day workshops allowed participants to explore physical models and computational approaches used for the simulation of biological systems and the investigation of their function at an atomic level. Designed for graduate students and postdoctoral researchers in computational and/or biophysical fields, the workshops introduced subjects such as force fields and algorithms used in molecular modeling, molecular dynamics simulations on parallel computers, and steered molecular dynamics simulations. The program of the workshop provided participants with conceptual lectures in the morning, followed by hands-on tutorial sessions in the afternoon. During the tutorial sessions, participants worked through tutorials in a hands-on fashion, utilizing text and files provided by the Resource, with needed software installed by participants on their laptops. Details of the workshops are as below:

- August 10–14, 2009 *Hands-on Workshop on Computational Biophysics*[*] - at this second workshop, 21 participants from academia, including two doctorates, came

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

from locations nearby (e.g., Chicago) and afar (Turkey) to pursue their interests in theoretical and computational biophysics. At this workshop, participants were given flexiblity in tutorial options, and even the option to pursue their own projects, during tutorial sessions. Results from the workshop evaluation are very positive, with 87% indicating the workshop improved their ability to carry out original research in the field of theoretical and computational biophysics, and 93% indicating the workshop met their expectations.

- July 6–10, 2009 *Hands-on Workshop on Computational Biophysics*[†] - at this workshop, 23 participants again came from as nearby as Champaign and from as far away as Chile and Germany to spend a week learning new techniques and methods applicable to their own research interests. Ten of the participants identified themselves as postdoctoral associates, and while most (19) were from academia, four of the participants came from non-profit entities. Evaluation results indicate that 90% felt that the workshop broadened their understanding of concepts and principles in the field of computational and theoretical biophysics, and 95% indicated the workshop addressed their research needs.

Collaborative Workshops. A "collaborative workshop" is defined by the Resource as an event in which involves significant contributions by the Resource (e.g., lectures, tutorials, funding, etc.) to a training event organized by an external group. Two such events occurred over the last funding period:

- January 14–17, 2010, *Cryo-EM Map Workshop*, National Center for Macromolecular Imaging, Houston, Texas[‡] - at this event, the Resource provided a day of lectures and tutorials, utilizing its new tutorials on molecular dynamics flexible fitting, and structure checking. Evaluation results show a high proportion, 81% of participants rated the quality of the lecture as positive, and 96% rated both the quality and utility of the tutorials positively.

- November 23–26, 2009, *Workshop on Molecular Simulation of Bio and Nano Particles*, Talca, Chile[§] - this workshop relied on Resource software (Visual Molecular Dynamics (VMD), Nanoscale Molecular Dynamics (NAMD) and tutorials on NAMD, membrane proteins, alchemical free perturbation and adaptive biasing force for its training program. As with the usual Resource workshop format, morning lectures related to the tutorials were followed in the afternoon by hands-on tutorial sessions.

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

[‡] `http://www.ks.uiuc.edu/Training/Workshop/Houston/index.html`

[§] `http://nanobiology.utalca.cl/workshop/`

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:

- *Molecular Dynamics Flexible Fitting* - this tutorial describes how to flexibly fit atomic structures into density maps using the MDFF method. This method can be used to obtain atomic models of macromolecular complexes by combining X-ray structures and cry-electron microscopy maps.
- *Structure Check* - this tutorial describes two VMD plugins that can be used to detect and correct certain structure errors, namely chirality and cis peptide bonds. The plugins can also be used to prevent these errors from occuring in simulations with NAMD.

Other Resource tutorials were checked and updated over the past 12 months, in preparation for workshop events, or for other training purposes.

Interest in the tutorials is high. As indicated by Resource web site statistics on views of the tutoral library, there were well over 75,000 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.

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 2009 - April 2010 there were nearly 6,000 views of the case studies, with the *Water and Ice* and *Membranes* case studies the most popular, as shown in Table 4.

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

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

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

Ten Most Viewed Tutorials	Views
VMD Tutorial	28,482
NAMD Tutorial	15,406
VMD Images and Movies	6,774
Building Gramicidin A	3,201
Parameterizing a Novel Residue	2,882
Topology File Tutorial	2,570
Simulation of Water Permeation through Nanotubes	2,381
Membrane Proteins	2,359
Stretching Deca-Alanine	1,685
Aquaporins with the VMD MultiSeq Tool	1,675
Total for all tutorials	75,783

Table 3: Views of online tutorials from May 2009 - April 2010

Case Study	Views
Water and Ice	874
DNA	834
Myoglobin	720
Structure of Ion Channels	709
Membranes	611
Light Harvesting Complex II	561
BPTI	475
Titin Ig Domains	385
Ubiquitin	380
Aquaporins	309
Total	5,858

Table 4: Views of case studies from May 2009 - April 2010

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 2009 - April 2010 period (listed by the month they started their visit) include:

- Ly Le, University of Utah (April 2009)

- Maria Musgaard, Aarhus University, Denmark (March 2010)
- Lei Wang, University of Science and Technology, China
- Fabien Archambault, Universite Henri Poincare, France (June 2009)
- Matt Chiu, Boston University (October 2009)
- Tristan Croll, Queensland University of Technology, Australia (September 2009)
- Angelica Fierro, University of Santiago, Chile (July 2009)
- Wei Jiang, Argonne National Laboratory (September 2009)
- Chalermpol Kanchanawarin, Kasetsart University, Thailand (September 2009)
- Ashfaq Khan, Boston University (October 2009)
- Qian Qian, University of Sheffield, United Kingdom (May 2009)
- Ilia Solov'yov, Johann Wolfgang Goethe University, Germany (July 2009)

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.

- Eduardo Cruz-Chu, Biophysics, University of Illinois, Spring 2010
- Leonardo Trabuco, Biophysics, University of Illinois, Spring 2010
- Lingling Miao, Physics, University of Illinois, Fall 2009
- Ying Yin, Physics, University of Illinois, Fall 2009

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

- Anton Arkhipov
- Peter Freddolino
- David Hardy
- Chris Harrison

- Barry Isralewitz
- Eric Lee
- Jan Saam
- Eduard Schreiner
- Melih Sener
- Amy Shih
- Xueqing Zou

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 2009 - Spring 2010 are listed below.

- Biomolecular Physics
- Statistical Physics
- Physical Chemistry
- Special Topics in Physics
- Computational Structural Biology
- Nonequilibrium Statistical Mechanics
- Medical Pharmacology
- Mechanics and Relativity

Resource Library

The Resource library, an important internal training resource, has been expanded by the purchase of 17 new books, bringing the total volume count to 1,060 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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