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   A. NAME: Klaus J. Schulten
   B. TITLE: Professor
   C. SIGNATURE:
6. DATE SIGNED (Month, Day, Year):
7. TELEPHONE NUMBER (Include Area Code): (217) 244-2212
8. FACSIMILE NUMBER (Include Area Code): (217) 244-6078
9. ELECTRONIC MAIL ADDRESS: `kschulte@ks.uiuc.edu`
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General Description of Resource Operation:

The Resource for Macromolecular Modeling and Bioinformatics develops computational tools for biomedical research in molecular cell biology and pharmacology. The tools combine biological science, physical science, computational and mathematical approaches and serve both wide applications and the most advanced ones. A particular emphasis of the Resource is to base its development on its own intense research program in biomedicine, thereby evolving its computational tools along with the frontiers of the field. The Resource engages into collaborations with leading experimental laboratories and carries out a highly popular training program in computational biology both through frequent face-to-face training workshops as well as through wide-spread on-line distribution of training material. Most notable is the continued proliferation of the Resource's software in the community that increases every year its already huge user base and sees many thousands of downloads for each new release.

The Resource derives its software development, training, and dissemination strengths through an outstanding technical staff whose many years of experience and technological contributions make staff members as highly regarded in the outside world as are the Resource's faculty leaders. Three core development areas focus on (1) the development of the molecular dynamics program NAMD, (2) on the development of the general sequence, structure, and modeling tool VMD, and (3) on developing molecular modeling/simulation tools for specific tasks in cell biology, such as the determination of very large structures through a combination of crystallography and electron microscopy or whole cell modeling.

As pointed out, the Resource's key strength is a combination of research and development. On the research side, the Resource is presently engaged in biomedical research at several fronts: fighting coronary diseases by advancing knowledge on cholesterol uptake by high density lipoproteins and on blood clotting factors, fighting viral infections by resolving the infection process of several viruses in unprecedented detail, furnishing 4th generation DNA sequencing for personalized medicine, and fighting cancer by understanding how DNA methylation changes gene regulation. The Resource is also engaged in groundbreaking research at the main frontiers of cell biology, from resolving the folding process of proteins in atomistic detail, to seeing the action of the ribosome – an important target for new antibiotics – in chemical detail, to providing images of how living cells shape their interior forms. Many thousand biomedical scientists from the bench to the world's most advanced computer centers utilize the Resource's software every day while high school, college, and graduate students utilize training and visualization material provided on the popular webpage to discover for themselves the miracles of living cells.

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. All projects

have been selected for their great scientific potential and, therefore, require fundamental advances of the available software tools, new algorithmic strategies, and even entirely new theoretical concepts. The Resource is particularly closely linked to two major research efforts, an NSF funded Center for the Physics of Living Cells (co-directed by Resource director K. Schulten) and an NIH-funded glue grant centered in Chicago studying membrane processes.

Close collaborations are also a key feature of the software developmental activities of the Resource. In the long history of these collaborations Resource staff always took advantage of new and emerging commodity technologies as well as leading edge technology. Presently, the use of cheap graphics processing units for general purpose computing is developed, vastly speeding up computations without cost increase. On a more costly and even more extreme scale, the power of new generation of petascale computers, coming on line presently at world-leading centers, is being harnessed by the Resource program NAMD, making possible simulations involving 100 million atoms as well as simulations lasting hundreds of microseconds at all atom resolution and of nearly a minute at coarse resolution. The Resource furnishes other solutions at the leading edge of technology, for example, in case of its program VMD the use of commodity stereographic 3D and multi-touch monitors.

The translation into robust, functioning, user friendly software comes about through Resource staff that is in charge of the actual software, turning requests from application scientists and strategies from computational scientists into modern software code that is continuously adapted to available 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 from the adoption of ever-new technologies. In the following the operation of the three Resource Cores are summarized.

Core-VMD. This TRD develops the software package VMD. VMD excels at visualizing large all-atom structures (over 100 million atoms) and long-time molecular dynamics trajectories. While originally developed as a companion program for the Resource's program NAMD to visualize molecular dynamics trajectories, VMD's unique modular design allows the incorporation of plugins that extend its capabilities into other areas such as bioinformatics, coarse grained representations of subcellular processes and bio nanodevices, and most recently for quantum chemistry and lattice cell simulations.

VMD continuous to be a very popular software program that is in high demand by biomedically and biologically oriented scientists: The most recent version of VMD, version 1.9, was released in March 2011. Since the release, over 7,200 users have registered and downloaded the program. The previous release of VMD, version 1.8.7, was released in

August 2009, and has over 54,500 users. Approximately 18% of the VMD user community is NIH-funded researchers. The main reasons for this unbroken demand are the continued effort of the Resource staff to improve the software and make it available and usable to researchers who are not by themselves computer scientists.

The main areas of improvement over the last reporting period are scene export features that enable researchers to create publication-quality renderings and movies of their molecular graphics. VMD now supports the X3D scene description format for the web, enabling exported molecular graphics to be interactively rotated and scaled in the latest web browsers without the need for installation of browser plugins, ideal for many education and research environments. Other improvements are aimed at increasing VMD's structure building capabilities and several new molecular dynamics analysis features. VMD general performance has also improved considerably and allows now viewing of even larger structures and longer trajectories.

Core-NAMD. This core develops NAMD, a parallel molecular dynamics code designed for high performance simulation of large biomolecular systems. In October 2010 a new version of NAMD, NAMD 2.7, was released and has been downloaded by over 4,600 users in only five months of which 800 of these users are NIH-funded. Since its first launch NAMD attracted over 44,000 registered users proving it to be one of the most popular and extremely useful codes for simulating large biological systems. NAMD is installed and used heavily on all major research computer centers across the globe.

The main area of improvement in the 2.7 release of NAMD is the greatly increased performance through graphics processor acceleration. Additional improvements made the software user friendlier and easier to handle for non-computer scientists. An intense development schedule led to a March 2011 release of NAMD in the form of NAMD 2.8b1 that offers further improved graphics processor acceleration, including now simulations with many cross-links as they arise in case of ribosome simulations and including type-pair specific non-bonded parameters as needed in modern force fields that account for atomic polarizability. NAMD 2.8b1 also greatly increased the size of the simulation that can be performed with a given amount of memory per node.

Core-Cell Biology Software. This core focuses on developing and implementing molecular modeling/simulation tools to study various cellular processes. Based on development in the VMD and NAMD cores, the tools in this core are designed for specific areas of computational studies of cellular biological systems and processes. This core develops the following software: Molecular Dynamics Flexible Fitting (MDFF) for structure analysis, Membrane Modeling Tools (MMT), Brownian Motion Tool (BMT), and Whole Cell Simulation Tool (WCST).

Molecular dynamics flexible fitting (MDFF) is a structure analysis method that combines crystallographic and cryo-EM data through computational modeling and is particularly well suited for very large structures. It was developed by Resource scientists to bridge the resolution gap between X-ray and cryo-EM data. The method is ideally suited for molecular cell biology as it can furnish very large structures as demonstrated through ribosome-membrane studies and ongoing poliovirus infection studies.

Membranes participate in almost all cellular processes and the MMT will serve to study these processes. Even though great advances in experimental structural biology have been made over recent years it became evident that static structures are not sufficient to fully characterize the function of membrane proteins, and in order to fully understand their mechanism, a dynamical description is necessary. Examples are cases of membrane channels only resolved structurally in their closed state. Resource scientists and developers devised various computational tools designed not only to study some of the technical issues currently hampering simulations of membrane processes, but also to provide a user-friendly interface for both novice and expert user. An important area of application is the study of antimicrobial peptides.

Many cellular processes take place at a multi-nanometer scale and the new BMT will assist researchers in studying dynamic processes at that scale, using geometrical and force input from VMD and NAMD. Currently, a stand-alone prototype of the tool exist that permits sub-millisecond simulations of realistic micron-size channels with atomic resolution of classical molecular dynamics. Using this prototype, Resource scientists have modeled transport of small solutes through sticky nanochannels, demonstrating that the Langmuir adsorption isotherm of a realistic heterogeneous surface can be accurately computed from the atomic structures of the solute and the channel's surface. Another area of ongoing application of BMT is engineering of nanopores for sequencing DNA, where the highly efficient yet atomically precise BMT was used to determine the ionic current signature of all possible permutations of the nucleotide sequence of a DNA strand in a nanopore. Written as a general purpose Brownian Dynamics software, its biomedical applications will include, but are not limited to, simulations of diffusive transport in the crowded environment of a cell, spontaneous association of biomacromolecules, transmembrane transport, and design of biomedical devices such as micro/nanofluidics lab-on-chip systems and synthetic blood vessels.

WCST is still at an early development stage, basically, only a prototype exists developed in an o going research project. The research focus is a study of random variation in gene expression between bacterial cells that affects cellular decision-making and leads to differences in the protein profile and phenotype among genetically identical bacteria. Advances in the measurement of individual protein and mRNA molecules inside living cells have provided the means to study how individual cells change their protein composition over

time. Resource scientists studied the lac genetic switch in E. coli to investigate random differences in gene expression. This switch is used by E. coli to find, collect, and process lactose from its environment. For the study a new computational method for describing the dynamics of a biochemical system undergoing diffusion and reaction, known as the reaction-diffusion master equation, was developed. Employing graphics processing unit acceleration computation experienced a dramatically speed-up. An important feature of the approach is its ability to describe whole bacterial cells including the effect of molecular crowding. The study, that has recently been published, is now turned into a software development effort leading to the WCST.

Collaborations, Service, Training and Dissemination. 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. To make access to the Resource even easier a new web-based inquiry form for new collaborations has been established that will enable interested scientists to get into contact with Resource researchers and developers in suggesting new projects.

The Resource's web site continues to be highly popular with over 700,000 unique visitors during the last year. The web site reaches out to all interested scientists and laypersons, giving access to a myriad of information and permitting download of the Resource software packages VMD and NAMD. Many of the Resource's users download this software repeatedly (for new releases) showing a steady and even growing interest in the service.

A key part of the Resource's service strategy is to be in direct contact with users of its software. One important part of this user support are email lists that offer users the possibility to interact with Resource staff directly to get helpful advice from developers and scientists. Equally popular are regularly offered workshops run by Resource faculty and staff. Five workshops were conducted during the last year in San Diego, Urbana (2), Atlanta and Pittsburgh. Surveys indicated clearly that this training is of great value to users.

During the last year Resource faculty published 66 papers, 12 more publications are in press. Many of these papers were published together with collaborators either on campus or off campus. Resource faculty had the opportunity to present their work in over 50 seminars at national and international universities and conferences.

The Resource received much attention form many news outlets. Of particular interest for the popular media were the Resource Director's keynote lecture at the NVIDIA GPU Technology Conference, and the Resource's work on cryptochrome and avian navigation which was covered by the Wired news site. Also popular were Dr. Aksimentiev's project on developing cheaper, faster method for DNA sequencing.

Highlights

MDFF

Structural information of biological systems is essential in order to understand the function of the system. For instance, determination of structures of the ribosome, a large molecular machine responsible for translating genetic information into proteins in cells, have provided important insights into the complex working mechanisms of the translation process. The importance of structural information in the study of translation is highlighted by the 2009 Nobel Prize in Chemistry awarded to three researchers for their contributions in solving ribosomal structures. Due to this crucial role of structural data in biological science, various experimental methods have been developed and used to obtain structure of biomolecules, for example, X-ray crystallography, cryo-electron microscopy (cryo-EM) and nuclear magnetic resonance.

Biomolecules adopt different conformations to perform different functions; it is difficult to obtain high resolution structures of biological systems in their functional form. The highest resolution experimental method for structure determination, namely X-ray crystallography, requires crystallization of molecules that can force them into conformations which are not necessary biologically functional. On the other hand, cryo-electron microscopy capture images of molecules in their different functional states, but at lower resolution than X-ray crystallography. Therefore, functional atomic resolution models of molecules, especially large molecular machines like the ribosome, are difficult to obtain by either of the two methods alone.

The molecular dynamics flexible fitting (MDFF) method was developed by Resource scientists to bridge the resolution gap between X-ray and cryo-EM data [1, 2].* MDFF guides the high resolution atomic structures obtained by X-ray crystallography towards the conformational states represented by the cryo-EM data of the molecules by incorporating the cryo-EM density map into molecular dynamics simulations. MDFF is based on the two main programs, VMD [3] and NAMD [4], developed by the Resource. MDFF has already been successfully applied to investigate the ribosome [5–13] and protein-induced membrane curvature [14, 15] through collaborations with leading cryo-EM laboratories in the world.

Resource scientists have continued to apply MDFF to study the ribosome. Several atomic structures of the ribosome in different functional conformations were obtained by MDFF. In collaboration with Joachim Frank (Columbia U., HHMI), Resource scientists applied MDFF to obtain the atomic models of the ribosome with cognate and near-cognate tRNAs during decoding (Fig. 1); the structures provided insights into the discrimination mechanism of the ribosome which ensures correct sequence synthesis [13]. The structure of the

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

ribosome-bound SecYEG complex, which is a protein-conducting channel for translocating nascent proteins across or into membranes (Fig. 1), was obtained by applying MDFF to cryo-EM data from our collaborators Rolland Beckmann (U. Munich, Germany) and the gating mechanisms of the protein-conducting channel was resolved [12]. In addition to giving structural insight into the functional properties of different conformational states, the MDFF models also provided starting structures for molecular dynamics simulations which are employed to further elucidate molecular mechanisms.

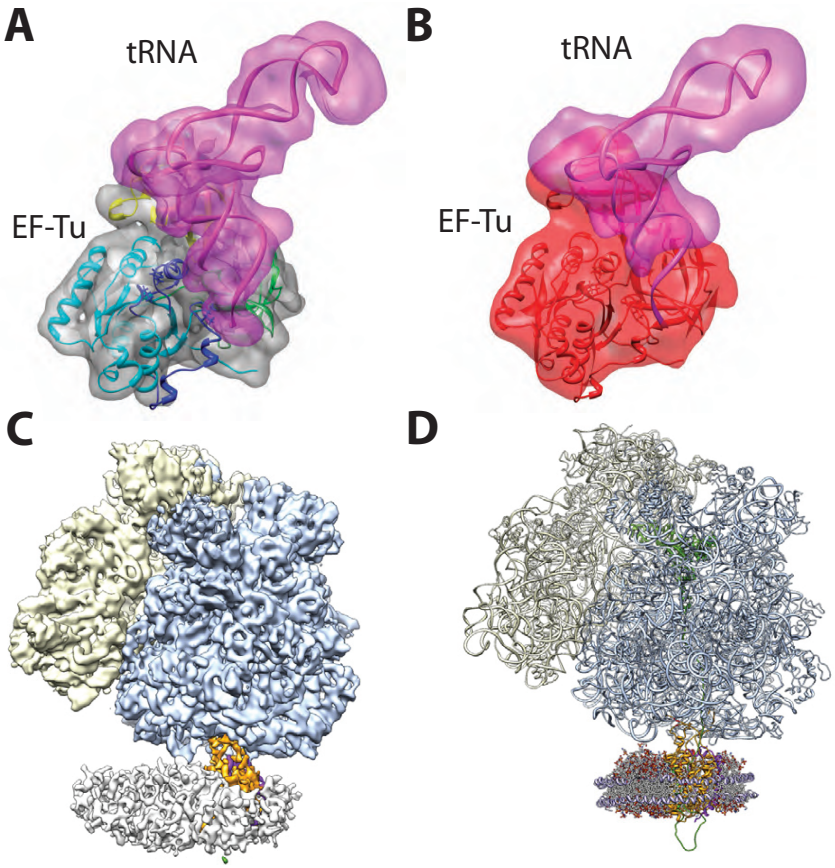

Figure 1: (A,B) Fitted atomic structure of ternary complex with (A) cognate and (B) near-cognate tRNAs respectively. (C) Electron microscopy image of the ribosome-bound SecY structure. (D) Atomic model of ribosome-bound SecYEG obtained by MDFF.

MDFF has proven a power technique for structural determination of biological systems and using NAMD for large-scale simulation and VMD for large-scale analysis, MDFF is even applicable to very large and complex systems like the ribosome. Resource scientists have successfully employed MDFF to investigate several aspects of ribosome function. MDFF is also currently employed by non-Resource scientists for structural analysis of different biological systems [16–21]. Driven by various applications, ongoing MDFF development continues to improve its speed and accuracy for merging multi-resolution structural data.

GPU Computing in Biomedicine

Over the last several years graphics processing units (GPUs) incorporated in personal computers have grown far beyond their original intended purpose and have become programmable computing devices capable of performing trillions of arithmetic operations per second. The Resource has begun to exploit GPUs for a revolutionary increase in biomedical computing power for biomolecular simulation, analysis, and visualization. The outcome of this effort, which is already well underway (first publication in 2007) and ahead of other similar efforts, promises to bring the computational power of compute clusters to laptops and to accelerate supercomputer calculations, as carried out by many NIH investigators, by a factor of 12 times or more[†]. GPUs have achieved significant penetration into the scientific computing community since the release of the CUDA programming system in 2007 by NVIDIA, a key GPU manufacturer with whom the Resource collaborates closely.

Several new GPU-accelerated analysis algorithms have been added to the Resource's molecular visualization and analysis tool VMD[‡], increasing performance for computationally demanding tasks such as calculation of electrostatic fields [22–28]. The GPU-accelerated analysis algorithms enable calculations that would have previously required a cluster of 50 or more traditional processor (i.e., CPU) cores to be performed on a single desktop computer containing one or more GPUs, making these capabilities accessible to researchers that lack the technical expertise to use cluster-based solutions and lowering the equipment costs required to do these calculations.

Many biomedical research projects rely on quantum chemistry calculations and there is high demand for the integration of the visualization of molecular orbitals and quantum chemical properties with large and complex models of biomolecules. The computations needed for the display of electron dynamics in large biomolecules are too expensive to allow interactive visualization at present. GPUs pose an opportunity for achieving the required speedup. The Resource has developed a functional prototype for the GPU-accelerated calculation of molecular orbitals, enabling interactive animation [29,30]. The key innovation is the ability to perform these calculations in fractions of a second, a hundred times faster than other tools available for the same purpose. The Resource is currently adapting these techniques to other computationally demanding visualizations that will enable researchers to see the dynamics of biomolecular structures in ways that were not possible before.

In order to address the most challenging scientific computing tasks, clusters of GPU-accelerated machines must be employed. To support the development of applications

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

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

for such clusters, the National Center for Supercomputing Applications (NCSA) has recently upgraded its existing GPU cluster. The Resource was able to demonstrate a factor of twelve overall speedup from GPU acceleration when running a million-atom NAMD[§] simulation on the entire cluster, performance equivalent to hundreds of traditional processors [31].

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

Flow-Induced Structural Transition of the GPIbα β-switch

The biological function of proteins is determined by their structures; the structure-function relationship is particularly interesting in case of proteins acting as sensors of environmental properties like flow, temperature, or ion concentration [32]. The glycoprotein Ibα (GPIbα), located on the surface of platelets, acts as a sensor of blood flow and plays an essential role in controlling blood clot formation in wound healing; deficiency or malfunction of the GPIbα protein results in bleeding disorders like the Bernard-Soulier syndrome [33–35] and type 2B von Willebrand disease [36].

Experimental evidence suggests that interaction between glycoprotein Ibα and another protein present in the blood plasma, the von Willebrand factor (vWF), initiates platelet adhesion to injured blood vessel walls, and that the adhesion is enhanced by blood flow [37]. Crystallography revealed a structural change of the β-switch region of GPIbα after it binds to vWF, e.g., its C-terminal region adopts an ordered hairpin conformation when binding to the vWF, while without such binding, it adopts a disordered loop conformation, as shown in Fig. 2. Since experiments cannot capture the intermediate conformations of the β-switch under flow conditions, so far it could not be proven directly that flow induces the loop to β-hairpin transition. Understanding the biological role of GPIbα in blood clotting requires a molecular-level description of its behavior under blood flow.

The Resource developed a molecular dynamics algorithm that serves to generate stable water flow under constant temperature to mimic physiological blood flow conditions [38].[¶] Flow dynamics simulation pushes a fraction of water molecules to generate flow, adapting the force to the desired flow velocity. The flow MD simulation has been successfully employed to investigate the kinetics of flow-induced β-hairpin formation of the glycoprotein Ibα β-switch [37–39]. Furthermore, the molecular dynamics algorithm generating stable flow within the solvent environment can be applied for other proteins, providing further opportunities for studies of protein structural transitions under flow condition.

The flow dynamics simulation was performed on the 17-residue β-switch region of glycoprotein Ibα, the region believed to undergo the flow-induced structural transition [37]. Comparison of the start and end structures reveals a conformational change in this region, clearly displaying a flow-induced loop to β-hairpin transition, agreeing with the hypothesis that the loop to β-hairpin transition in GPIbα is induced by flow before binding to von Willebrand factor. Fig. 2 shows snapshots of the β-switch intermediates during the loop to β-hairpin transition. The results reveal that the free energy landscape of the β-switch has two stable conformations, loop and hairpin, imprinted on it, and flow induces a transition between the two.

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

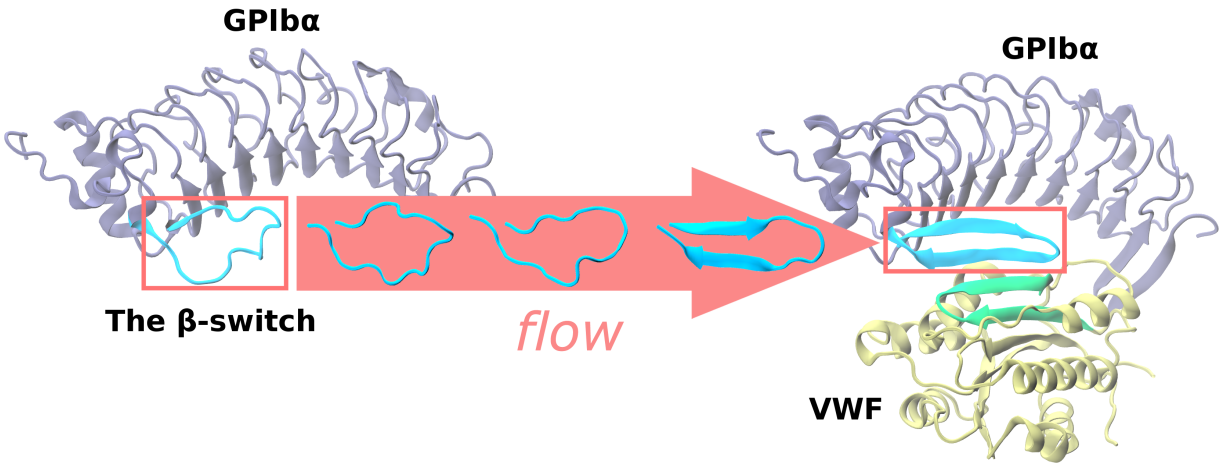

Figure 2: Flow-induced loop to β-hairpin transition on the β-switch of GPIbα. The β-switch adopts a loop conformation before binding to VWF. Flow induces the β-switch to transit from a disordered loop to an ordered β-hairpin, enhancing the binding of GPIbα to VWF.

The study on flow-induced β-hairpin transition elucidates the molecular mechanism of a blood flow sensor. The β-switch of GPIbα adopts a loop conformation without flow; once a blood vessel is damaged, bleeding-caused shear flow triggers the β-hairpin folding of the GPIbα β-switch; this conformational change increases the binding affinity of GPIbα to von Willebrand factor and eventually leads to blood clotting which is the first step in healing the vessel. An atomic description of flow-induced hairpin formation in the β-switch will aid to uncover the molecular mechanism underlying bleeding disorders, such as type 2B von Willebrand factor disease, caused by mutations in the β-switch.

Muscle Elasticity

Muscle cells function like elastic springs that generate forces when stretched or compressed, thus allowing animals to move. Integral to their correct functioning is that they remain structurally sound and have safeguards in place to prevent severe damage. Multiple proteins found in muscle cells act in concert to achieve this functioning, including the largest and longest protein known to date - a giant protein called titin. Titin spans the whole muscle cell and acts like a spring that returns the muscle to its resting length after contraction and is thought to act as a shock absorber to prevent irreparable muscle injury. Titin has also been connected with muscular diseases such as myasthenia gravis, where muscles get significantly weaker with activity, and hypertrophic cardiomyopathy, the leading cause of sudden cardiac death in young athletes.

An understanding of how the constituent parts of muscle cells respond to mechanical forces provides us insight into how muscle cells carry out their function and how they attain their remarkable elasticity. In particular, to investigate the functioning of titin, which simultaneously acts as a molecular spring and is able to absorb sudden extreme forces, it is necessary to be able to stretch the protein in a controlled manner and analyze its behaviour.

Molecular dynamics, due to its atomic level accuracy and high degree of control of the system dynamics that it offers, is ideally suited to studying titin. Resources scientists have previously developed a method by which the response of proteins to force can be investigated using constant velocity pulling or constant force pulling, known as steered molecular dynamics (SMD) [40, 41]. Using SMD, resource scientists have in the past investigated a single domain of titin to elucidate how its spontaneous unravelling at a peak force, termed the rupture force, enables titin to function as a muscular shock absorber [42–44].[‖] Titin, however, is not only a shock absorber but also acts as a molecular spring. To investigate this part of the function, the structure of a multi-domain segment of titin was determined by Resource collaborator Prof. Olga Mayans (Univ. Liverpool). Resource scientists were able to calculate the force response of this much larger structure using all-atom SMD simulations enabled by NAMD [4].

The results of SMD simulations allowed Resource scientists to identify the structural foundations of the spring-like behavior of titin [45]. It was shown that multiple degrees of freedom, such as inter-domain bending and individual domain stretching, taken together are responsible for titin's elastic response to external forces. Furthermore, it was shown that to capture the correct force response the effect of viscous drag due to the surrounding water molecules needs to be eliminated. This is only possible when slow pulling velocities (which in turn require long simulation times) are used in SMD simulations [46]. These

[‖] URL: http://www.ks.uiuc.edu/Research/smd_imd/titin

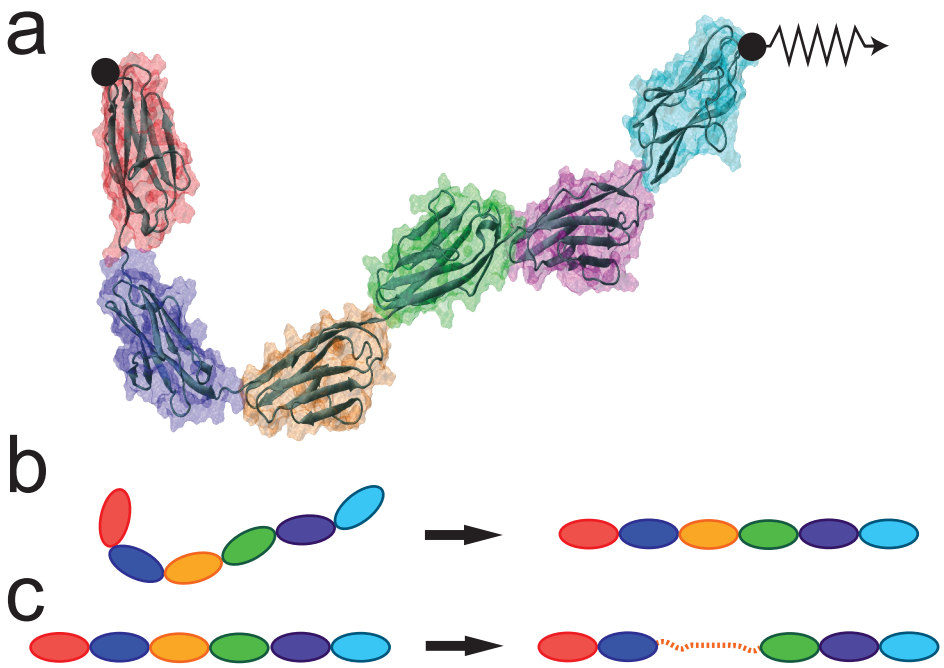

Figure 3: (a) Six-domain segment of titin. Steered molecular dynamics pulls one end of the structure while holding the other fixed. (b) The first force response of titin is to straighten out from its relaxed state, providing the muscle with its so-called passive elasticity. (c) The second force response of titin is to unravel individual domains which quickly provides additional length, thus acting as a shock absorber.

simulations led to the development of a simple, yet highly accurate theoretical description of titin elasticity [45–47].

All-atom SMD simulations using slow pulling velocities have elucidated how the structure of titin enables a two-mode response to applied forces. This dual force response provides muscles with a high degree of structural stability and mechanical elasticity.

Whole-cell Simulation of In Vivo Reaction Diffusion Processes

Expressing genes in a bacterial cell is noisy and random. A colony of bacteria grown from a single cell can show remarkable differences in the copy numbers per cell of a given protein after only a few generations. Such differences originate from random variation in gene expression between cells and can affect cellular decision-making. In some circumstances, these random decisions can lead to microbial populations that, while genetically identical, nevertheless appear to be split when observed for specific traits. Recently, advances in the measurement of individual protein and mRNA molecules inside living cells have provided the means to study how individual cells change their protein composition over time. Likewise, reconstruction and analysis of individual cells using cryoelectron tomography (CET) have provided data on the location of key large molecules inside the cell, such as the ribosomes.

In a recent study, Resource scientists and their collaborators at the Max Planck Institute of Biochemistry used computer simulations to study the variation in how individual cells in a population express a set of genes in response to an environmental signal. The modeled system was the *lac* genetic switch that *Escherichia coli* uses to find, collect, and process lactose sugar from the environment. The model was based on data from single-molecule and biochemical experiments along with CET structural data, as shown in Fig. 4. The noise inherent in the genetic circuit controlling the cell's response determines how similar the cells are to each other and the Resource scientists studied how the different components of the circuit affected this noise. Furthermore, an estimated $30 - 50\%$ of the cell volume is taken up by a wide variety of large biomolecules. To study the response of the circuit caused by such crowding, they simulated the circuit inside a three-dimensional model of an *E. coli* cell built using data from CET reconstructions of a single cell and proteomics studies. The authors report [48] that correctly including random effects of molecular crowding will be critical to developing fully dynamic models of living cells.

To enable this study, Resource scientists developed a new computational method for simulating the equation that describes the dynamics of a biochemical system undergoing diffusion and reaction, known as the reaction-diffusion master equation (RDME). Using the computational power provided by graphics processing units (GPUs) they were able to dramatically speed up the calculations associated with simulating the RDME when accounting for crowding in the cellular environment [49]. By extending the size of the modeled system to encompass the entire cell and the time covered by the simulation to the order of a cell cycle (approximately one hour), the new method enables biomedical researchers to study aspects of cellular regulation and control that were previously off limits.

The new method marks an important step in computational modeling of whole cells. It will allow Resource and other researchers to integrate data from structural, single-

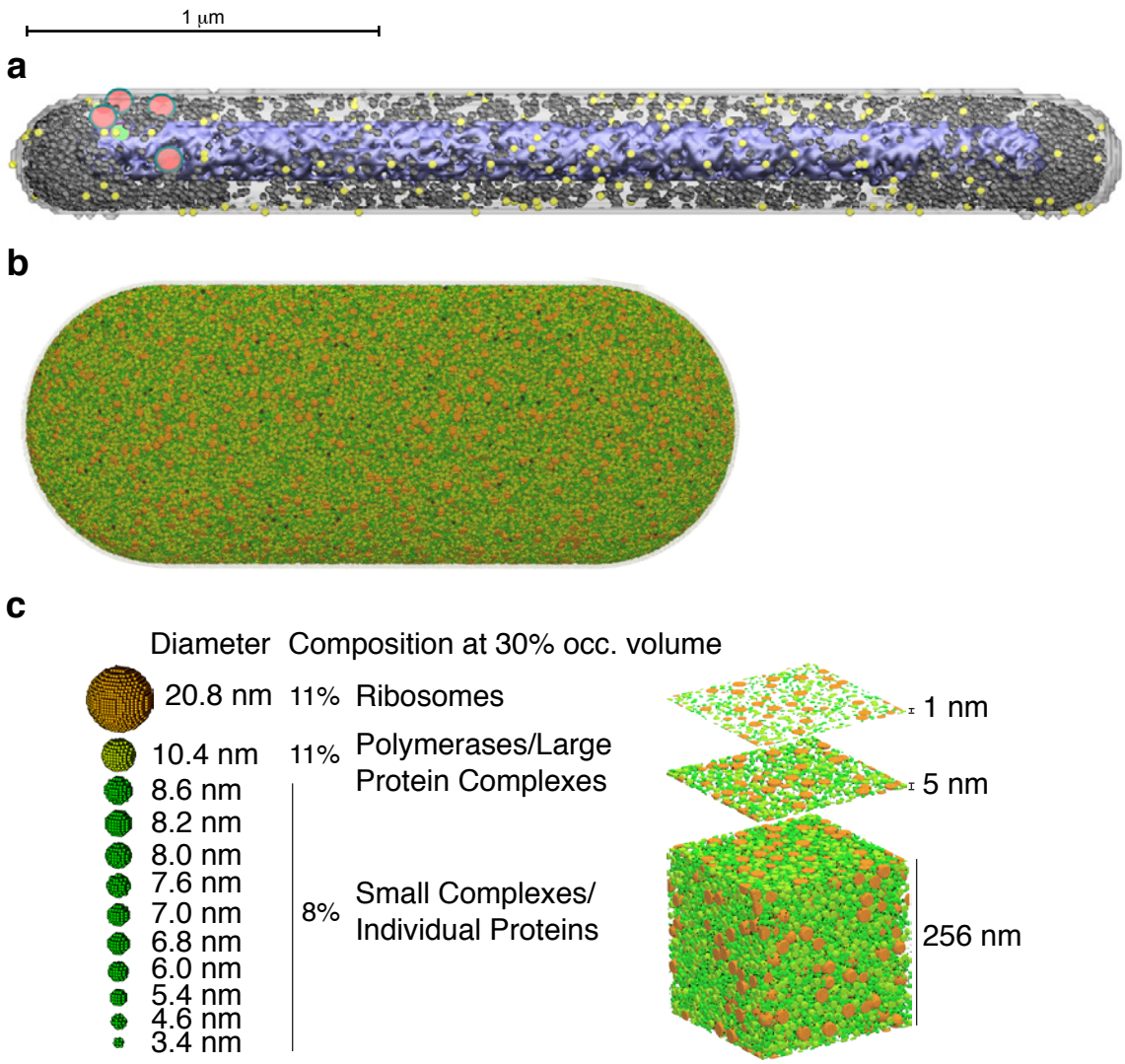

Figure 4: (a) Frame from a simulation of the production of a lactose transporter protein (yellow circles) in a slowly growing *E. coli* in response to lactose in the environment. Grey circles are ribosomes and pink circles are messenger RNA. The green circle is the repressor molecule that shuts down transcription when it binds to the sugar transporter gene in the bacterial DNA (purple zone). (b) Model of a fast growing *E. coli* showing the full packing of the cytoplasm. (c) Composition of large obstacles inside the *E. coli* cytoplasm as determined from proteomics data.

molecule, and biochemical studies of cells into coherent computational models. Currently, Resource research continues on further improvements to the method as well as modeling of additional cellular processes, such as cell division.

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Subprojects

BTA UNIT: C

TITLE: Membrane Protein Structural Dynamics Consortium

KEYWORDS: Membrane proteins, membrane channels, membrane transporters, molecular dynamics, lipid-protein interaction, large protein conformational changes

INVEST1: Emad Tajkhorshid
DEGREE1: PhD
DEPT1: Biochemistry and Beckman Institute
NONHOST1:

INVEST2: Klaus Schulten
DEGREE2: PhD
DEPT2: Biochemistry and Beckman Institute
NONHOST2:

INVEST3: Wei Han
DEGREE3: PhD
DEPT3: Beckman Institute
NONHOST3:

INVEST4: Wenxun Gan
DEGREE4: PhD
DEPT4: Beckman Institute
NONHOST4:

INVEST5: Christopher Mayne
DEGREE5: PhD
DEPT5: Beckman Institute
NONHOST5:

INVEST6: Benoit Roux
DEGREE6: PhD
DEPT6: Biochemistry and Molecular Biology
NONHOST6: University of Chicago

INVEST7: Harel Weinstein
DEGREE7: PhD
DEPT7: Biophysics and Physiology

NONHOST7: Cornell University

INVEST8: Ivet Bahar

DEGREE8: PhD

DEPT8: computational and Systmes Biology

NONHOST8: University of Pittsburgh

INVEST9: Hassane Mchaourab

DEGREE9: PhD

DEPT9: Molecular Physiology and Biophysics

NONHOST9: Vanderbilt University

INVEST10: Robert Nakamoto

DEGREE10: PhD

DEPT10: Biochemistry and Molecular Genetics

NONHOST10: University of Virginia

INVEST11: Merritt Maduke

DEGREE11: PhD

DEPT11: Molecular and Cellular Physiology

NONHOST11: Stanford University

% BTA $: BTA %

ABSTRACT: Membrane proteins play an essential role in the exchange of material and information between living cells and their environment, the flow and use of energy, and in numerous signaling pathways. As such, they participate in almost all cellular processes fundamental to the living, development, and well being of cells and organisms. 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 in order to fully understand their mechanism, a dynamical description is necessary. Conformational and interaction dynamics have a large impact 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 is required to understand the complex web of signaling and energy transduction mechanisms involved both in 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, the Resource joined 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)" (http://memprotein.org) was formed and funded through a "Glue Grant" by the NIH National Institute of General Medical Sciences in 2010. 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 study major mechanistic questions associated with membrane protein function in 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.

The Resource participates in this broad activity by contributing to the Computational Core of the MPSDC, which is considered the "glue" of the consortium and is in charge of designing and implementing novel computational approaches to link static and dynamic data with function. Through these tools, the Core plays a key role in integration of the experimental and simulation data obtained from different methodologies into dynamical structural models describing the nature of conformational changes in the studied membrane proteins. The Computational Core is also in charge of developing and establishing standardized protocols for rapid and objective optimization of accurate force fields at different levels of resolution. Such force field parameters are key to the simulations that include, e.g., non-standard amino acids, drugs, and other ligands. The Computational Core also investigates and implements more efficient methods to study transition between different conformational states using simulation technologies. The Resource participates in and contributes to all these areas.

In addition to the Computational Core, the Resource members are also in charge of the computational component of a number of specific projects, namely "Conformational dynamics in the CLC channel/transporter family" and "Structural dynamics of ABC transporters". In both projects, the large-scale simulations performed by the Resource are used to interpret the results of experimental measurements per-

formed by the collaborating laboratories, and to design the next step of the experiments in which novel hypotheses obtained developed by the simulations will be tested. In the CLC project, currently, the dynamical differences between monomeric and dimeric forms of the channel and the effect of various lipid environments of the protein's dynamics are currently investigated by the Resource. Structural and dynamical differences identified through these simulations will be used as a basis for NMR studies in the collaborating lab (Merritt Maduke, Stanford). In the ABC transporter project, the focus is on P-Glycoprotein (PGP), a key transporter involved in development of resistance in cancer cells. The structural changes observed through the simulations of the membrane-bound model of this transporter under different conditions have bee used to identify the areas of the protein that would respond maximally to EPR measurements, both in terms of structural fluctuation and distance changes. These results have been communicated to the collaborating lab (Hassane Mchaourab, Vanderbilt) who is currently working on labeling the protein at the identified sites and to perform EPR measurements on the designed mutants.

BTA UNIT: T

TITLE: Scalable Molecular Dynamics Software NAMD

KEYWORDS: molecular dynamics simulation, high-performance computing

INVEST1: James Phillips
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Chris Harrison
DEGREE2: Ph.D.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: David Hardy
DEGREE3: Ph.D.
DEPT3: Beckman Institute
NONHOST3:

INVEST4: Ryan McGreevy
DEGREE4: B.S.
DEPT4: Beckman Institute
NONHOST4:

INVEST5: Laxmikant Kale
DEGREE5: Ph.D.
DEPT5: Computer Science
NONHOST5:

INVEST6: Eric Bohm
DEGREE6: B.S.
DEPT6: Computer Science
NONHOST6:

INVEST7: David Kunzman
DEGREE7: M.S.
DEPT7: Computer Science
NONHOST7:

INVEST8: Chao Mei

DEGREE8: M.S.

DEPT8: Computer Science

NONHOST8:

INVEST9: Yanhua Sun

DEGREE9: M.S.

DEPT9: Computer Science

NONHOST9:

INVEST10: David Tanner

DEGREE10: B.S.

DEPT10: Biophysics

NONHOST10:

% BTA $: BTA %

ABSTRACT: NAMD (Nanoscale Molecular Dynamics, http://www.ks.uiuc.edu/Research/namd/) is a parallel molecular dynamics code designed for high performance simulation of large biomolecular systems [1, 2]. NAMD employs the prioritized message-driven execution capabilities of the Charm++/Converse parallel runtime system (http://charm.cs.uiuc.edu/), allowing excellent parallel scaling on both massively parallel supercomputers and commodity workstation clusters. NAMD is distributed free of charge to over 44,000 registered users as both source code and convenient precompiled binaries. 11,700 users have downloaded multiple releases. The 2005 NAMD reference paper [2] has been cited over 1500 times. NAMD 2.7 was released in October 2010 and has been downloaded by over 4,600 users, 800 NIH-funded.

NAMD 2.7 builds on NAMD 2.7b2 from November 2009 by adding 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 allows our collaborators to complete tests needed to validate the force field in a timely manner. NAMD 2.7 provides increased performance for CUDA graphics processor acceleration through block-based pairlists that reduce the amount of time spent finding atoms within the cutoff distance. Released NAMD 2.7 Linux binaries include direct support for high-performance InfiniBand networks via the OFED "ibverbs" library, eliminating the need for users to build Charm++ and NAMD against a local MPI installation to use increasingly common InfiniBand hardware, but can be launched using any MPI launch program (mpirun or mpiexec) that is already supported on the machine, simplifying the scripts required to run jobs under the control of a queuing system.

NAMD 2.8b1, released in March 2011, adds support for the generalized Born implicit solvent model, the accelerated molecular dynamics method, the MARTINI residue-based coarse-grain forcefield, non-uniform grids in grid forces, new symmetry and domain restraints, and force output and trajectory files. The load balancer in NAMD 2.8b1 performs measurement-based grain-size adjustment, enabling scaling to over 1000 cores for large implicit solvent simulations while reducing overhead for simulations on small processor counts. Graphics processor acceleration is more flexible, supporting simulations with many cross-links such as the ribosome and type-pair specific nonbonded parameters as needed by the Drude force field. Released binaries are now provided for Microsoft Windows HPC Server.

NAMD 2.8b1 greatly increases the size of simulation that can be performed with a given amount of memory per node via three advances. First, released "SMP" (shared-memory parallelism) binaries use threads to allow multiple processor cores on a node to share large molecular data structures of which each core would previously have a private copy while offloading communication to a single thread. Pure SMP, or "multicore" binaries, dispense with inter-node communication completely for further efficiency and ease of use on isolated workstations. For simulations that do not fit into per-node memory even with SMP mode, experimental memory-optimized builds now include parallel I/O for further memory reduction and increased scalability. Finally, a hybrid load balancer eliminates the need to collect all load information on a single node by applying the NAMD centralized load balancer strategies independently to groups of 512 cores. The combination of SMP, memory optimization, parallel I/O, and hybrid load balancing now allows a simulation of 100 million atoms to run on a 16,384-node IBM BlueGene/P with only 2 GB of memory per node and to scale to all 224,076 cores of a Cray XT5 at ORNL.

BTA UNIT: T

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

KEYWORDS:

INVEST1: John Stone
DEGREE1: M.S.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Kirby Vandivort
DEGREE2: M.S.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: Zaida Luthey-Schulten
DEGREE3: Ph.D.
DEPT3: School of Chemical Sciences
NONHOST3:

INVEST4: Elijah Roberts
DEGREE4: Ph.D.
DEPT4: Center for Biophysics and Computational Biology
NONHOST4:

INVEST5: John Eargle
DEGREE5: B.A.
DEPT5: Center for Biophysics and Computational Biology
NONHOST5:

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ABSTRACT: VMD [3] 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 computational and graphical performance, and the graphical user interfaces have been revised to make the program more intuitive and easier to use. VMD 1.9, the most recent version, was released on March 14, 2011.

Many improvements have been made to the VMD scene export features that enable researchers to create publication-quality renderings and movies of their molecular graphics. The latest VMD release can export molecular scenes to the Wavefront .obj scene format with graphical representation material and grouping information, and in a more compact form that makes it much easier to load large molecular complexes into commercial rendering and animation tools such as Maya. VMD now supports the X3D scene description format for the web, enabling exported molecular graphics to be interactively rotated and scaled in the latest web browsers without the need for installation of browser plugins, ideal for many education and research environments.

VMD incorporates many improvements aimed at increasing its structure building capabilities. The latest version of the molefacture plugin performs geometry optimizations and can assign charges using the latest versions of SQM and Antechamber (distributed with AmberTools). Molefacture now allows structures to be built for the OPLS force field, based on included CHARMM-formatted OPLS parameter files. Molefacture also provides an FEP setup tool to aid in the generation of structures and input files for free-energy perturbation simulations with NAMD. New Chirality and Cispeptide plugins help researchers build their structures by detecting, visualizing, correcting, and enforcing chirality and peptide bond configuration in proteins. A new tutorial describing the Cispeptide and Chirality plugins is also available.

VMD also includes several new molecular dynamics analysis features. The new ParseFEP plugin provides a set of tools for analyzing free-energy perturbation (FEP) calculations performed with NAMD. The PLUMED plugin allows collective variable analysis from within VMD, using PLUMED. VMD includes a new GPU-accelerated method for computing radial distribution functions up to 90 times faster than with the CPU alone. The updated Timeline plugin provides an interface for viewing temporally changing per-residue attributes of a molecular structure. It can also display temporally changing attributes of a set of VMD atom selections, for example a set of all the salt-bridge pairs observed in a trajectory. The latest version of Timeline also improves performance for large structures and long trajectories, provides more analysis functions and options, and significantly improves the printing

features for saving trajectory analysis plots as encapsulated Postscript (.eps) files. The latest version of the MultiSeq [4] plugin adds support the use of MAFFT for multiple alignments, and improves performance over previous versions, allowing up to 100,000 sequences to be loaded, aligned, and displayed on a desktop workstation.

Over 54,500 users have registered for VMD 1.8.7 since it was released on August 1, 2009. Over 3,200 users downloaded pre-release beta test versions of VMD 1.9 over a 30 day period prior to the final release. VMD 1.9 was released on March 14, 2011, and has already been downloaded by over 8,100 users.

BTA UNIT: T

TITLE: NAMD-Lite and Molecular Simulation Methods Development

KEYWORDS: molecular dynamics simulation, methods development

INVEST1: David J. Hardy
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Charles L. Brooks
DEGREE2: Ph.D.
DEPT2: Departments of Chemistry and Biophysics
NONHOST2: University of Michigan

INVEST3: Alexander D. MacKerell, Jr.
DEGREE3: Ph.D.
DEPT3: Department of Pharmaceutical Sciences, School of Pharmacy
NONHOST3: University of Maryland

INVEST4: Benoit Roux
DEGREE4: Ph.D.
DEPT4: Biochemistry and Molecular Biology
NONHOST4: University of Chicago

INVEST5: Robert D. Skeel
DEGREE5: Ph.D.
DEPT5: Department of Computer Science
NONHOST5: Purdue University

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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 (MSM), implemented in NAMD-Lite, offers fast linear scaling calculation of electrostatics for both periodic and nonperiodic boundary conditions [5,6]. GPU acceleration of the most computationally expensive parts of the MSM [7,8] and subsequent integration into VMD [3] (http://www.ks.uiuc.edu/Research/vmd/) has made it feasible to calculate electrostatic potential maps across entire simulation trajectories (e.g., leading to better understanding of the drug resistance of the H1N1 virus [9]). The NAMD-Lite implementation of MSM can now utilize GPUs for calculating the electrostatic forces needed for molecular dynamics. Ongoing work in collaboration with Robert Skeel includes development of a distributed memory parallelization of MSM for its inclusion into NAMD [2] (http://www.ks.uiuc.edu/Research/namd/) and extending the MSM to calculate the dispersion forces. Other future developments include using NAMD-Lite as a fast energy evaluation tool for VMD and as a single-node GPU-accelerated tool, coupled to VMD, to perform interactive molecular dynamics [10].

NAMD-Lite has also assisted the Resource in implementing better force field models. The fidelity of biomolecular simulation is improved by modeling electronic polarizability of atoms to account for the electron density response to an electric field. A polarizable force field based on classical Drude oscillators [11] is being developed by collaborators Benoit Roux and Alexander MacKerell. The Drude model was initially prototyped in NAMD-Lite before its parallelization into NAMD. The novel use of a dual-temperature Langevin thermostat for dynamical simulation of the Drude oscillators enables NAMD to achieve efficient parallel scaling of the Drude model with computational cost that is not more than twice that of the standard force field model without polarizability [12]. An alternative model for electronic polarizability using fluctuating charges [13,14] has also been implemented into NAMD, in collaboration with Charles Brooks' NIH Research Resource Center for Multiscale Modeling Tools in Structural Biology.

BTA UNIT: C

TITLE: Computational Facility

KEYWORDS: parallel computing, visualization, network

INVEST1: Haley Mui
DEGREE1: B.S.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: John Stone
DEGREE2: M.S.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: James Phillips
DEGREE3: Ph.D.
DEPT3: Beckman Institute
NONHOST3:

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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/Computers/)

The Resource has benefited greatly from the 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 was 31 million service units for this past year. The Resource has also been awarded 4 million service units through the Institute for Advanced Computing Applications and Technologies funded by the State of Illinois. These allocations are supplemented by the Resource clusters.

In pursuit of continued technological developments for high performance molecular dynamics simulation, the Resource has worked to improve its computational

facility and resources. The Resource has offered large memory computational resources as a part of its computational facility for many years. These resources have proven to be very valuable in the hands of Resource scientists and collaborators. In order to meet the increased demand, the Resource has added two additional machines to its computational facility. Each machine provides 48 processing cores with 256 GB of RAM. One of these machines is further supplemented with an Nvidia S2050 GPU system giving the machine four GPUs (Graphical Processing Units). This upgrade allows for greater computational capacity and bolsters the Resource's continuing efforts in developing GPU-accelerated versions of the NAMD [2] (http://www.ks.uiuc.edu/Research/namd/) and VMD [3] (http://www.ks.uiuc.edu/Research/vmd) packages. Additionally, the Resource is currently working on supplementing its existing 8-node GPU cluster with another 8-node cluster boasting faster processors, increased RAM, and Nvidia C2050 GPUs.

Support for the general collaborations, 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. These new workstations features 8 processing cores with 72 GB of RAM, Nvidia GeForce graphics high resolution 30 inch displays and stereoscopic 3D LCD panels. Additionally, Resource scientists have been provided with upgraded workstations with high resolution 30 inch displays. These workstations boast a quad core Intel Xeon processor with 24 GB of Random Access Memory (RAM) and high end Nvidia GeForce graphics.

The Resource has operated visualization facilities for its scientists and collaborators for many years. The high resolution (1920 by 1200) stereoscopic projection system installed last year has proven very valuable to the Resource. This past year, the Resource has supplemented this system with an even higher resolution projection system (4096 by 2400) to provide visualization of even higher resolution images and movies generated by Resource research.

The Resource has added three storage servers boasting 48 2-TB hard drives increasing its total networked storage capacity to 500 TB (compared to 200 TB last year). This will allow the Resource to further increase disk space for Resource collaborations. The Resource will also continue to upgrade 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. 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: Structural Analysis of the Ribosome

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

INVEST1: Leonardo G. Trabuco
DEGREE1: Ph.D.
DEPT1: CellNetworks
NONHOST1: University of Heidelberg, Germany

INVEST2: Christopher B. Harrison
DEGREE2: Ph.D.
DEPT2: Beckman Institute for Advanced Science and Technology
NONHOST2:

INVEST3: Eduard Schreiner
DEGREE3: Ph.D.
DEPT3: Beckman Institute for Advanced Science and Technology
NONHOST3:

INVEST4: Joachim Frank
DEGREE4: Ph.D.
DEPT4: Howard Hughes Medical Institute
NONHOST4: Wadsworth Center, NY

INVEST5: Kwok-Yan Chan
DEGREE5: B.S.
DEPT5: Physics
NONHOST5:

INVEST6: Bo Liu
DEGREE6: M.S.
DEPT6: Center for Biophysics and Computational Biology
NONHOST6:

% BTA $: BTA %

ABSTRACT: The ribosome is the molecular machine responsible for translating genetic material into functional proteins (http://www.ks.uiuc.edu/Research/ribosome/). Ribosomes exist in all cells, constituting up to half of the net dry weight. Over 50% of the research effort on antibiotics is focused on the ribosome because of its biological significance [15]. During translation, the ribosome assembles, with very high fidelity, the amino acid sequence encoded by the sequence of a bound mRNA molecule: successive mRNA codons are accurately matched to the anti-codons of cognate tRNAs charged with amino acids; incoming amino acids are added to a growing polypeptide chain, mRNA with paired tRNA is translocated through the ribosome, and the uncharged tRNA is released. To understand the mechanism of translation, we examine several of these key processes, and the attendant roles of catalyzing protein factors.

To assure that proteins are synthesized with their correct sequences, the ribosome must be able to differentiate a cognate tRNA, which carries the correct amino acid, from a non-cognate tRNA. By applying MDFF simulations in explicit solvent, Resource scientists determined the atomic model of the ribosome bound with a cognate tRNA Cryo-EM map at 8.25 Angstrom resolution and the ribosomal structure with a non-cognate tRNA Cryo-EM map at 13.2 Angstrom resolution. The tRNA:EF-Tu:GTP complexes of those two models were closely compared. Structural differences showed the molecular foundations responsible for the high fidelity of ribosomal translation [16]. During translation, the ribosome fluctuates between the ratcheted and the non-ratcheted states to facilitate the translocation of the tRNA-mRNA pairs from the A site, where the tRNA initially binds the ribosome, through the P site, where the nascent protein chain is elongated, to the E site, where the tRNA is released by the ribosome. During translocation, the tRNA also must fluctuate between the classical and the hybrid states to fulfill its function. MDFF contributed to solving atomic models of the ratcheted ribosome interacting with a hybrid state (P/E) tRNA-Phe and with a hybrid state (P/E) tRNA-fMet. With extensive equilibrium MD simulations and statistical analysis, Resource scientists showed that tRNA-Phe, an elongator tRNA, interacts more strongly with the ribosome compared with tRNA-fMet, which is the initiator tRNA. Resource scientists applied Targeted Molecular Dynamics simulations to drive the opening motion of the L1 stalk, a ribosomal structure located at the E site. The results showed that the L1 stalk can facilitate tRNA release [17]. Finally, Resource scientists derived an atomic model for the elongation factor EF-G, which is a GTPase facilitating translocation, by fitting the atomic coordinates of EF-G obtained from X-ray crystallography into a cryo-EM map of a EF-G-bound ribosome. Further extensive MD simulations showed that the ability of the EF-G domains to undergo large conformational changes is crucial to its functions [18].

BTA UNIT: C

TITLE: The Protein-Conducting Channel

KEYWORDS: translocon, SecY, protein channel, ribosome, free energy cost

INVEST1: James Gumbart
DEGREE1: Ph.D.
DEPT1: Physics
NONHOST1:

INVEST2: Leonardo G. Trabuco
DEGREE2: Ph.D.
DEPT2: CellNetworks
NONHOST2: University of Heidelberg, Germany

INVEST3: Eduard Schreiner
DEGREE3: Ph.D.
DEPT3: Beckman Institute for Advanced Science and Technology
NONHOST3:

INVEST4: Roland Beckmann
DEGREE4: Ph.D.
DEPT4: Gene Center, Department of Chemistry and Biochemistry
NONHOST4: University of Munich, Germany

INVEST5: Chris Chipot
DEGREE5: Ph.D.
DEPT5: Beckman Institute for Advanced Science and Technology
NONHOST5:

% BTA $: BTA %

ABSTRACT: Proteins are synthesized and excreted by the ribosome to their proper cellular environment. For membrane proteins, the ribosome needs to collaborate with protein-conducting channel(PCC) to deliver the nascent unfolded protein chain into the membrane.(http://www.ks.uiuc.edu/Research/translocon/) For bacteria, the ribosome bounds the PCC complex called SecYEG, which is embedded in the membrane, to form such secretory pathways, which event is triggered by the presence of signal anchor sequence during translation. The ribosome-docked PCC cotranslationally facilitates translocation and integration of the nascent secretory proteins in the membrane environment.

To understand the molecular mechanism dictating the co-translational translocation process facilited by the Sec complex, the Resource scientists applied MDFF to solve the atomic structure of the ribosome-bound SecYEG complex in the lipid environment. The complex was reconstituted into the Nanodiscs structure which enables researchers to determine a cryo-EM map of the complex at 7.1 Angstrom resolution [19]. MD simulations based on the MDFF-determined structure further showed that 30S of the ribosome spontaneously modulates the membranes surrounding SecYEG complex, facilitating lipids to open the proposed lateral gate of the PCC [19]. Using free-energy perturbation calculations, the Resource scientists determined the effective transfer free energies from the translocon to the membrane for the arginine and leucine amino acids carried by a back-ground polyleucine helix. The results support a two-step insertion process of the nascent protein into membranes by the ribosome in which insertion into the translocon is energized by the protein synthesis and insertion into the membrane associates a free energy cost of the translocon-helix system comparing favorably with experimental results [20].

BTA UNIT: T

TITLE: Acceleration of Molecular Modeling Applications with Graphics Processors

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

INVEST1: David Hardy
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: James Phillips
DEGREE2: Ph.D.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: John Stone
DEGREE3: M.S.
DEPT3: Beckman Institute
NONHOST3:

INVEST4: Kirby Vandivort
DEGREE4: M.S.
DEPT4: Beckman Institute
NONHOST4:

% BTA $: BTA %

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 multi-core CPUs. 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 [7, 8, 21–23], yield 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 [3].

GPU acceleration techniques have also 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 [24, 25], the use of GPUs is 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 [21, 26]. Support for GPU acceleration in NAMD has been extended to include block-based pairlists and calculation of the full pressure tensor in NAMD 2.7 and type-pair specific nonbonded parameters in NAMD 2.8b1.

The Resource has also developed new algorithms to accelerate visualization of molecular orbitals through the use of GPU computing [27, 28]. The latest implementation released in VMD 1.9 supports both CUDA and OpenCL GPU computing toolkits enabling the acceleration on GPUs made by several vendors. The use of multiple GPUs in parallel has achieved hundred-fold speedups over conventional multi-core CPUs, enabling interactive visualization of molecular orbitals calculated on-the-fly from the wavefunction data. The development of this feature serves as a basis for interactive visualization of other molecular properties that also have computational demands that cannot be met by traditional techniques.

BTA UNIT: C

TITLE: Molecular Dynamics Simulations of Protein Folding

KEYWORDS: protein folding, lambda repressor, high pressure

INVEST1: Yanxin Liu
DEGREE1: M.S.
DEPT1: Physics
NONHOST1:

INVEST2: Martin Gruebele
DEGREE2: Ph.D
DEPT2: Chemistry
NONHOST2:

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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). Studies on 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, thanks to advances in parallel molecular dynamics simulations, the full folding process of small proteins can now be studied computationally (http://www.ks.uiuc.edu/Research/folding).

The Resource has made a great effort to study two model proteins over the past few years: the villin headpiece sub-domain and Pin1 WW domain [29–33]. The current focus is on another fast folding protein with more complicated native topology, namely lambda-repressor fragment. It is a five-helix bundle protein with experimentally known folding time less than 15 microseconds for some of its mutants. Simulation of the lambda-repressor in explicit solvent involves a system containing more than 70,000 atoms, and requires 10-20 microseconds in duration to observe complete folding events. The necessary simulation timescales was obtained by using the molecular dynamics program NAMD developed by the Resource [2], which has been optimized to deliver performance of 150 ns per day on the folding system [29,31,33]. 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.

A series of MD folding simulations were performed on lambda-repressor including a fast-folding mutant under pressure-jump experiment (lambda-YG) and a fast-folding mutant under temperature-jump experiment (lambda-HG). The lambda-YG mutant refolds into the native state in 2 microseconds in pressure-jump experiment, close to the "speed limit". We carried out molecular dynamics simulations under different temperatures and pressures to address the question of why refolding from the pressure denatured state is so much faster than refolding upon temperature jump for lambda-YG mutant. We found that both the unfolding pathway and native stability depend on temperature and pressure. The simulations show that the helices I and IV are the most stable elements. Rapid nucleation of helices I and IV is proposed to be a major factor in enhancing the refolding rate once the pressure is dropped to 1 atm. To identify an ensemble of truly high-pressure denatured states that are responsible for the ultrafast refolding in pressure jump experiment, we subsequently drop the temperature in the unfolding simulation, but maintain the high pressure. The disrupted secondary structure recovered rapidly in less than 100 ns and the equilibrated high-pressure denatured protein adapts a compact structure as indicated by small radius of gyration with high secondary content. Both factors contribute to the fast refolding dynamics in pressure jump experiments. We are currently performing simulations to directly observe the refolding events under ambient pressure.

The Resource also received allocation of Anton machine from PSC together with Martin Gruebele to perform simulations on the fast folding mutant lambda-HG. Two trajectories with aggregated simulation time of 30 microseconds have been generated. Although the complete folding events are not observed in the simulations, two major kinetic traps are identified through cluster analysis. The proposed mutants, designed to fold faster by removing two kinetic traps, are being tested experimentally in Martin Gruebele's lab.

BTA UNIT: C

TITLE: Timeline: a VMD plugin for trajectory analysis

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

INVEST1: Barry Isralewitz
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: John Stone
DEGREE2: M.S.
DEPT2: Beckman Institute
NONHOST2:

% BTA $: BTA %

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 result is a plot of the calculated property against simulation time and structural component axes, allowing 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 [3] 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 March 2011 release of VMD 1.9; over the past year the Resource has made several important additions to Timeline. Added built-in analysis functions make the plugin more powerful and more useful for new or occasional users; new GUI-based analysis parameter entry allows much more convenient exploration of how adjusting parameters of built-in functions affects the whole-trajectory graph. High-quality printing has been added, which renders the various non-standard graph features of the plugin to a publication-ready .eps file. Improvements to handling large molecular systems have been made, as well as additions and improvements to the user interface, such as a live display of threshold data for the current selection. The resource has also released a Timeline tutorial to introduce new users to the plugin, instruct them in the use of basic features, and teach more advanced uses. In the coming year, the Resource plans to accelerate Timeline analysis computation by taking advantage of multi-core and GPU acceleration, and by adding an interface for remote parallel job spawning; also planned are features for multiple-trajectory and multiple-data set calculation and display.

BTA UNIT: C

TITLE: Gating and Function of the Mechanosensitive Channel MscS

KEYWORDS: MscS, mechanosensitive channel, osmosis, pressure sensitive channel

INVEST1: Ramya Gamini
DEGREE1: M.Sc.
DEPT1: Center for Biophysics and Computational Biology
NONHOST1:

INVEST2: Marcos Sotomayor
DEGREE2: Ph.D
DEPT2: Department of Neurobiology
NONHOST2: Harvard Medical School

INVEST3: Eduardo Peruzo
DEGREE3: Ph.D
DEPT3: Institute of Molecular Pediatric Sciences
NONHOST3: University of Chicago

% BTA $: BTA %

ABSTRACT: ABSTRACT

Mechanosensitive (MS) ion channels serve as molecular switches, opening and closing in response to stress conveyed through the cellular membrane [34,35]. In bacteria, MS channels of small conductance (MscS) are thought to act as safety valves preventing cell burst upon osmotic shocks [36,37]. (http://www.ks.uiuc.edu/Research/MscSchannel The two crystal structures of MscS [38–40], although representing different putative states of the transmembrane (TM) domain, depict the same architecture for MscS' large cytoplasmic domain (CD).

The MscS consists of a large cytoplasmic domain (CD) that features a balloon-like, water filled chamber with seven side openings. The side openings are the only gateway for water and cytoplasmic solutes to reach the cell exterior. Various studies have suggested that the CD plays a role in channel gating, stability and conductivity [41–46]. We propose, however, another function of the CD, namely that of a sieve that retains solutes valuable to the cell. We propose that the CD of MscS functions as an entropic filter slowing down osmolytes thus to prevent the passage of osmolytes, such as glutamate, to escape from a bacterial cell during hypotonic stress. The filter properties are such that the number of osmolyte molecules passing

through the filter is limited largely by the area of the seven side openings compared to the area of the entire CD and also modulated by a weak long-range interaction with the overall negative charge of the filter. We employ diffusion theory and MD simulations to explore the transport kinetics of Glu^- and K^+ as representative osmolytes. We suggest that the CD indeed acts as a filter that balances passage of positive and negative osmolytes in equal proportion to render the osmolyte translocation electrically neutral and, thereby, reduce cell depolarization in the open state and conserve to a large degree the essential metabolite glutamate [47].

BTA UNIT: C

TITLE: MDFF Development

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

INVEST1: Ryan McGreevy
DEGREE1: B.A.
DEPT1: Beckman Institute for Advanced Science and Technology
NONHOST1:

INVEST2: Leonardo G. Trabuco
DEGREE2: Ph.D.
DEPT2: CellNetworks
NONHOST2: University of Heidelberg, Germany

INVEST3: Eduard Schreiner
DEGREE3: Ph.D.
DEPT3: Beckman Institute for Advanced Science and Technology
NONHOST3:

INVEST4: Kwok-Yan Chan
DEGREE4: B.S.
DEPT4: Physics
NONHOST4:

INVEST5: Bo Liu
DEGREE5: M.S.
DEPT5: Center for Biophysics and Computational Biology
NONHOST5:

% BTA $: BTA %

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) [48, 49], 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 [50].

Over the past year, new types of restraints for MDFF have been developed to improve fitting by preserving certain structural elements of molecules during MDFF simulations. Domain restraints apply harmonic forces to user-defined groups of atoms to semi-rigidly fit individual domains of the molecules to the density. Symmetry restraints can be applied to groups of atoms defined by symmetrical relationships to enforce the symmetry during MDFF simulations. The MDFF test set, consisting of different types of biomolecules in different conformational states, has been utilized for parameter optimization. A new feature of NAMD, generalized Born implicit solvent, has been used in conjunction with MDFF to increase simulation speed and improve results over simulations done in vacuum. The implicit solvent model allows accelerated fitting by eliminating the viscous drag felt by the biomolecule from explicit water atoms. A new MDFF method driven by cross correlation has been prototyped; cross correlation MDFF uses forces from gradients of localized cross correlations between a simulated density map of the current molecular structure and the experimental Cryo-EM map. Further work is planned for refining the cross correlation MDFF method as well as increased testing and application.

BTA UNIT: C

TITLE: Physical Properties of Methylated DNA

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

INVEST1: Xueqing Zou
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Gregory Timp
DEGREE2: Ph.D.
DEPT2: Electrical and Computer Engineering
NONHOST2: University of Notre Dame

INVEST3: Philip Sevrin
DEGREE3: B.Sc.
DEPT3: Center for Nanoscience and Department of Physics
NONHOST3: University of Munich

INVEST4: Hermann E.Gaub
DEGREE4: Ph.D.
DEPT4: Center for Nanoscience and Department of Physics
NONHOST4: University of Munich

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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 [51]. 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 [52, 53].

One of the Resource's collaborator, Gregory Timp, discriminated methylated DNA and non-methylated DNA using synthetic nanopores [54]. Another collaborator, Hermann E. Gaub, measured different forces needed to rupture fully-methylated

DNA (fDNA), center-methylated DNA (cDNA) and non-methylated DNA (nDNA). Both experiments suggested that methylation changes the mechanical property of DNA. In the past year, to further characterize in atomic detail how DNA mechanical stability arising from epigenetic modifications, namely methylation, depends on quantity and sequence context of methylation sites, the Resource conducted a series of steered molecular dynamics simulations on fDNA, cDNA and nDNA to examine methylation-dependent strand separation of DNA and dynamics of DNA along its transition pathway between duplex state and strand separated state. In these simulations, fDNA, cDNA and nDNA were observed to undergo a B-DNA to zipper-like DNA transition during force-induced strand separation, zipper-like methylated DNA containing less faults, called bubbles, than zipper-like non-methylated DNA does; the concentration of bubbles was seen to control the propensity for strand separation such that methylation influences strongly the rupture force of DNA duplexes pulled at their two 5' ends. By monitoring length and stacking energy of DNA during strand separation, three significantly different separation pathways were identified for nDNA, cDNA and fDNA. The differences are attributed to the enhanced stacking interaction between methylated cytosine and its adjacent bases. Indeed, the stacking energy increases due to the additional methyl group on cytosine, reduces internal bubble formation and tightens the ends of DNA. As a result, rupturing methylated DNA requires a stronger force than rupturing non-methylated DNA. The simulations provided a detailed view of methylation effects on strand separation, revealing the underlying physical mechanism.

BTA UNIT: T

TITLE: Membrane sculpting by BAR domains

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

INVEST1: Hang Yu

DEGREE1: B.S.

DEPT1: Center for Biophysics and Computational Biology

NONHOST1:

% BTA $: BTA %

ABSTRACT: Proteins from the BAR domain superfamily [55], 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 [56, 57] from low-curvature liposomes. BAR domains form banana-shaped homodimers bearing a high density of positively charged residues on the concave surface [58–60], which facilitates sculpting of negatively charged membranes. However, single BAR domains induce only local membrane curvature [61, 62], while recent cryo-EM reconstructions [57] 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 [62, 63]. 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 mechanisms for 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 performed in concert, i.e., a multiscale approach.

In the past year, a 3.3 million atom, 250 ns all-atom simulation, together with a 1 millisecond coarse-grained model simulations probed the dynamics of F-BAR domain lattices in atomic detail. 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. A highly detailed, dynamic picture of the 100-microsecond formation of membrane tubes by lattices of F-BAR domains was obtained. Membrane bending by F-BAR domains was found to arise from electrostatic attraction between the positively charged concave surface of F-BAR domain and negatively charged lipid head group. For the first time, the simulations showed that F-BAR domain lattices drive membrane curvature not only by scaffolding, but also with its intrinsic helices flexibility. 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: Stepping Mechanism of Molecular Motor Protein Myosin

KEYWORDS: Myosin VI, Dimerization, Lever Arm, Steered Molecular Dynamics

INVEST1: Yanxin Liu
DEGREE1: M.S
DEPT1: Physics
NONHOST1:

INVEST2: Jen Hsin
DEGREE2: Ph.D
DEPT2: Physics
NONHOST2:

INVEST3: Hyeongjun Kim
DEGREE3: Ph.D
DEPT3: Physics
NONHOST3:

INVEST4: Paul R. Selvin
DEGREE4: Ph.D
DEPT4: Physics
NONHOST4:

% BTA $: BTA %

ABSTRACT: ABSTRACT

Motor proteins are found in almost all eukaryotic cells. They convert chemical energy from ATP hydrolysis to mechanical work that power muscle contraction and directional movement along cytoskeletal tracks. Over the years, the structural basis of how the motor proteins work has been established by solving the X-ray and cryo-EM structure for different domains of several motor proteins. What remains missing is the dynamic process connecting different states of motor protein's catalytic cycle. By teaming up with experts of single-molecule techniques from the Selvin lab here at UIUC, we hope to gain a molecular understanding of the stepping mechanism of motor protein (http://www.ks.uiuc.edu/Research/motor).

The Resource is currently involved in the study of one unique member of the motor protein myosin superfamily, namely Myosin VI. It walks towards the opposite direction along actin filaments compared to all other myosins. Despite its short lever

arm, whose length is usually proportional to its step size, myosin VI takes large steps. Some of the structural elements in its tail domain must act as a lever are extension to realize the large step size [64]. We are able to identify that the medial tail domain is a dimerization region, therefore does not contribute to the step size. The dimerization is mediated by the alternating opposite charged residues [65]. Residue-based coarse-grained (RBCG) model in NAMD [66, 67] was employed to reach the microsecond timescale needed for the self-assembly process of myosin VI medial tail domain. The molecular dynamics flexible fitting (MDFF) method was used to reverse the coarse-grained model into full atomic resolution [48, 49], revealing important interactions that stabilize the dimer conformation. The results were confirmed by single molecule experiments performed in Paul Selvin lab.

Since the dimerized medial tail domain does not contribute to the large step size that myosin VI takes, the proximal tail domain next to the lever arm must unfold and act as a lever arm extension. We performed steered molecular dynamics simulations to extend the proximal tail domain. Indeed, the proximal tail domain readily unfolded with secondary structure remains intact [68]. Lever arm binding calmodulin plays a key role in redirecting the force and maintaining the secondary structure of the proximal tail domain. The unfolding pathway was characterized, as well as prediction of extended conformation. Two calmodulin binding sites within the proximal tail domain open up during the unfolding process. We proposed that additional calmodulin binding may occur to mechanically strengthen the extended proximal tail domain [68].

BTA UNIT: C

TITLE: Multiscale Elasticity in the Muscle Protein Titin

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

INVEST1: Johan Strümpfer
DEGREE1: M.Sc.
DEPT1: Biophysics
NONHOST1:

INVEST2: Eric H. Lee
DEGREE2: Ph.D.
DEPT2: Medicine and Biophysics
NONHOST2:

INVEST3: Jen Hsin
DEGREE3: Ph.D.
DEPT3: Bioengineering
NONHOST3: Stanford, CA

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

% BTA $: BTA %

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 [69–75] and computer simulations [76–81] which have shed light on how the structure of titin resist mechanical stretching forces. Recent studies by Resource scientists have addressed the timescale gap between experiment and simulation and demonstrated that, although they are performed on different timescaled, they are probing the same molecular mechanisms [82].

Secondary structure elasticity (i.e. the unravelling of individual domains) has been extensively studied in the past. In contrast, tertiary structure elasticity (.e. the

elasticity arising from inter-domain interactions) is less understood. Given that tertiary structure elasticity is physiologically relevant in muscle functioning (whereas the role of secondary structure elasticity of the Ig domains is still being debated (9)), more attention is needed for titin's tertiary structure elastic response. Resource scientists showed in a recent study [83] that by reducing the velocity with which titin is stretched during simulations, the tertiary structure elasticity of a titin Ig-chain, directly involved in the physiological functioning of muscle, is observed in its totality as the hydrodynamic drag force is sufficiently decreased.

BTA UNIT: C

TITLE: Molecular Dynamics simulations of the omega current in voltage-gated potassium channels

KEYWORDS: K channel, shaker, omega current, ion channels

INVEST1: Fatemeh Khalili-Araghi
DEGREE1: Ph.D.
DEPT1: Physics
NONHOST1:

INVEST2: Emad Tajkhorshid
DEGREE2: Ph.D.
DEPT2: Biochemistry
NONHOST2:

INVEST3: Benoit Roux
DEGREE3: Ph.D.
DEPT3: Biochemistry and Molecular Biophysics
NONHOST3: University of Chicago

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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 cells 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 [84]. Kv channels 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 smaller Na+ ions) [84]. In addition to electrical signaling in nervous system, Kv channels play an important role in the regulation of cardiac excitability and regulation of insulin release. In humans, malfunction of these channels can result in neurological or cardiovascular diseases such as long QT syndrome or episodic ataxia [85].

In collaboration with Yarov-Yarovoy and Roux labs, the Resource has developed atomic models of the active and resting states of the Kv1.2 potassium channel [86].

These models proved to be in very good agreement with experimental constraints, indicating that they are representatives of the two functional states of the protein. In a separate study, the permeation of ions through an alternative pore (omega-pore) within the channel has been investigated using molecular dynamics simulations. The omega pore runs parallel to the main conduction pore, and is permeable to small cationic currents upon certain mutations of the channel [87]. The simulations identified the permeation pathway of K+ and Cl- ions through these pores, and allowed visualization of these pathways for the first time. The ions flow through aqueous crevices formed within the voltage-sensor domains of the protein. A narrow constriction region in the middle of the protein has been identified in the simulations to act as a plug against ion flow. The constriction region is lined with aromatic and negatively charged residue side chains which provide an energy barrier for incoming anions such as Cl- while attracting positively charged K+ ions.

BTA UNIT: T

TITLE: MultiSeq: Sequence and Structure Analysis Software

KEYWORDS: sequence, structure, software

INVEST1: Zaida Luthey-Schulten
DEGREE1: Ph.D.
DEPT1: School of Chemical Sciences
NONHOST1:

INVEST2: Elijah Roberts
DEGREE2: B.S.
DEPT2: Center for Biophysics and Computational Biology
NONHOST2:

INVEST3: John Eargle
DEGREE3: B.A.
DEPT3: Center for Biophysics and Computational Biology
NONHOST3:

INVEST4: Ke Chen
DEGREE4: B.A.
DEPT4: Center for Biophysics and Computational Biology
NONHOST4:

INVEST5: John Stone
DEGREE5: M.S.
DEPT5: Beckman Institute
NONHOST5:

INVEST6: Kirby Vandivort
DEGREE6: M.S.
DEPT6: Beckman Institute
NONHOST6:

% BTA $: %

ABSTRACT: MultiSeq [4] (`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. MultiSeq now supports the MAFFT multiple sequence alignment tool, which offers fast multiple alignment methods and can be used anywhere within MultiSeq that, previously, clustalw is used. MultiSeq was also updated to work with large (over 100,000) numbers of sequences. The MultiSeq window can now import RNA secondary structure definitions stored in the space-efficient bracket notation.

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 work with the 3DNA tools on RNA.

BTA UNIT: C

TITLE: The Photosynthetic Chromatophore

KEYWORDS: photosynthesis, quantum efficiency, chromatophore, protein distance constraint

INVEST1: Danielle Chandler
DEGREE1: B.S.
DEPT1: Beckman Institute for Advanced Science and Technology
NONHOST1:

INVEST2: Johan Strümpfer
DEGREE2: B.S.
DEPT2: Beckman Institute for Advanced Science and Technology
NONHOST2:

INVEST3: Jen Hsin
DEGREE3: Ph.D.
DEPT3: Beckman Institute for Advanced Science and Technology
NONHOST3:

INVEST4: Melih Şener
DEGREE4: Ph.D.
DEPT4: Beckman Institute for Advanced Science and Technology
NONHOST4:

INVEST5: Christopher B. Harrison
DEGREE5: Ph.D.
DEPT5: Beckman Institute for Advanced Science and Technology
NONHOST5:

INVEST6: Neil Hunter
DEGREE6: Ph.D.
DEPT6: Department of Molecular Biology and Biotechnology
NONHOST6: University of Sheffield, Sheffield, UK

INVEST7: Arvi Freiberg
DEGREE7: Ph.D.
DEPT7: Institute of Molecular and Cell Biology
NONHOST7: University of Tartu, Tartu, Estonia

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ABSTRACT: The chromatophore is a biological machine performing photosynthesis in purple bacteria. (http://www.ks.uiuc.edu/Research/psures/).

Photosynthesis is performed by specialized (pseudo-)organelles containing up to hundreds of proteins cooperating in a multi-step process of energy transfer, charge separation, quinone diffusion, and ATP synthesis [88]. In the purple bacterium *Rhodobacter sphaeroides* the photosynthetic apparatus is organized into chromatophore vesicles of nearly spherical shape of approximately 60 nm diameter that are mainly populated by dimeric core (RC-LH1-PufX) and antenna (LH2) complexes.

The architecture of the chromatophore has been determined [89] by combining atomic force microscopy, spectroscopy, crystallography, and electron microscropy studies improving upon an earlier model [90]. The absorption spectrum of low-light adapted chromatophores has been used to determine the stoichiometry of constituent proteins, revealing a LH2:RC ratio of 2.9:1. Additionally, curvature properties of the RC-LH1-PufX dimer core complex that had been determined by the MDFF method [91] is incorporated into the chromatophore architecture. Lastly, the packing density of LH2 units inaccurately reflected by the overpacking during sample preparation for AFM imaging [92] is accounted in the new chromatophore model. Generalized Foerster formulation has been used for rapid computation of energy transfer rates between pairs of complexes and subsequently across the network of hundreds of light harvesting proteins.

Important to the efficient capture of solar energy is the first nanosecond after which captured photon energy dissipates. During this time, multiple rapid inter-protein excitation transfer events occur to ensure that the solar energy can be stored more stably before it dissipates. By implementing computationally demanding dissipative quantum dynamics calculations, Resource scientists were able to elucidate how these rapid transfer events occur [93,94]. Further, an improved model of the noisy thermal environment was developed to elucidate the effect of correlated thermal fluctuations on the environment has on excitation transfer [95].

BTA UNIT: T

TITLE: Petascale Molecular Dynamics Data Processing

KEYWORDS: petascale simulation analysis, molecular modeling software

INVEST1: David Hardy
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Barry Isralewitz
DEGREE2: Ph.D.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: James Phillips
DEGREE3: Ph.D.
DEPT3: Beckman Institute
NONHOST3:

INVEST4: John Stone
DEGREE4: M.S.
DEPT4: Beckman Institute
NONHOST4:

INVEST5: Kirby Vandivort
DEGREE5: M.S.
DEPT5: Beckman Institute
NONHOST5:

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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 (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 microsecond, 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 exceeds 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, 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 Supercomputing 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.

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 and cluster nodes. VMD supports multi-core CPUs using multithreading, and supports GPUs and other many-core accelerator devices using CUDA, and the new industry standard OpenCL interface. The GPU algorithms in VMD increase performance for computationally demanding tasks such as calculation of electrostatic fields [7, 8, 21, 23, 26, 96, 97], calculation of radial distribution functions, and computation and display of molecular orbitals for visualization of quantum chemistry simulations [22, 27]. In order to help address the computational demands of analysis of petascale molecular dynamics simulations, VMD has been adapted to support execution on clusters and supercomputers using MPI, an industry-standard parallel processing system. The new VMD 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, all without requiring scientists to become parallel processing experts. These analysis features are incorporated into the most recent VMD 1.9 version released in March, 2011.

BTA UNIT: C

TITLE: Hepatitus C p7 viroporin

KEYWORDS: p7, HCV, viroporins, molecular dynamics flexible fitting

INVEST1: Danielle Chandler
DEGREE1: M.S.
DEPT1: Physics
NONHOST1:

INVEST2: Christophe Chipot
DEGREE2: Ph.D
DEPT2: Beckman Institute
NONHOST2: Nancy Université, France

% BTA $: BTA %

ABSTRACT: Hepatitis C virus (HCV) infection is a major, global health problem and a leading cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. The HCV p7 protein is a small integral membrane protein of 63 amino acids which oligomerizes and forms cation-selective pores. It has recently been demonstrated that p7 ion channel activity is required for the effective assembly and release of nascent HCV virions [98]. There is no crystal structure of p7, however, models based on experimental data have been explored. The p7 monomer forms two antiparallel transmembrane segments connected by a conserved cytosolic charged loop region, with both the N- and C-termini facing the lumen of the endoplasmic reticulum [99]. p7 oligomers have been observed in both heptameric and hexameric forms [100–102], and several hypothetical models of the p7 complex based on secondary-structure predictions have been reported [100, 102–104]. Most recently, a low-resolution cryo-EM map of p7 in a short-tail lipid environment (DHPC) by Luik et al. revealed a flower-like hexameric structure [102].

Oligomeric p7 models were constructed with four to seven subunits, which were tested via MD simulations in a hydrated POPC bilayer. These simulations allowed Resource scientists to determine the basic requirements for forming a functional p7 channel, including the optimal number of monomers. We also explored a route to reconcile these models with the flower-like motif seen by Luik et al [102]. It was found that the most stable and energetically favorable models were a hexameric and heptameric model in which adjacent monomers were arranged to optimize contact. The tetrameric and pentameric models were also stable; although p7 has never been observed as a tetramer or a pentamer, such structures may be viable, possibly as

intermediate stages in p7 self-assembly prior to the formation of the final hexameric or heptameric complexes. Each of the oligomeric models formed a pore which was accessible to solvent. The pore was open for the entire simulation for all cases except for the hexamer, which was initially closed, eventually opening 65 ns into the trajectory. In the hexameric model, the pore was initially blocked at the level of ILE32 and PHE25, suggesting that these residues could be involved in a possible gating mechanism for p7. The hexameric model was fitted into the 16 Å cryo-EM map of Luik et al. using the Molecular Dynamics Flexible Fitting method. The resulting structure was placed in both a POPC and a DHPC membrane and allowed to equilibrate. Once driven into the EM envelope and simulated by MD in the thin DHPC environment utilized in the experiment, the simulated structure largely retains its bent original conformation. Conversely, if placed in a POPC environment, which would more closely resemble the native membrane, the helices begin to straighten up as the structure progressively evolves towards a more upright conformation. Put together, these results illuminate the structural plasticity of the p7 monomer in an oligomeric context, and its adaptability to the membrane bilayer thickness.

BTA UNIT: T

TITLE: Petascale Biomolecular Simulation

KEYWORDS: molecular dynamics simulation, high-performance computing

INVEST1: James Phillips
DEGREE1: Ph.D.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Chris Harrison
DEGREE2: Ph.D.
DEPT2: Beckman Institute
NONHOST2:

INVEST3: Laxmikant Kale
DEGREE3: Ph.D.
DEPT3: Computer Science
NONHOST3:

INVEST4: Eric Bohm
DEGREE4: B.S.
DEPT4: Computer Science
NONHOST4:

INVEST5: Gengbin Zheng
DEGREE5: Ph.D.
DEPT5: Computer Science
NONHOST5:

INVEST6: Chao Mei
DEGREE6: M.S.
DEPT6: Computer Science
NONHOST6:

INVEST7: Yanhua Sun
DEGREE7: M.S.
DEPT7: Computer Science
NONHOST7:

INVEST8: Robert Brunner

DEGREE8: B.S.

DEPT8: NCSA

NONHOST8:

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ABSTRACT: The Resource is preparing both software and hardware to utilize the NSF-funded Blue Waters (http://www.ncsa.illinois.edu/BlueWaters/) IBM POWER7 sustained petascale computing system to be installed on campus in 2011. A simulation of 100 million atoms using NAMD (http://www.ks.uiuc.edu/Research/namd/) is specified as an acceptance test for the machine and the Resource was competitively awarded one of the first Petascale Computing Resource Allocations, which will be used to explore protein elongation in the ribosome, structural transitions in poliovirus entry, sculpting cellular membranes by BAR domains, and energy conversion by the chromatophore organelle. To support these simulations, the Resource was also competitively awarded an NIH small equipment grant that has been used 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.

In order to accommodate petascale simulations, the recently released NAMD 2.8b1 greatly increases the size of simulation that can be performed with a given amount of memory per node via three advances. First, "SMP" (shared-memory parallelism) builds use threads to allow multiple processor cores on a node to share large molecular data structures of which each core would previously have a private copy while offloading communication to a single thread. For simulations that do not fit into per-node memory even with SMP mode, experimental memory-optimized builds now include parallel I/O for further memory reduction and increased scalability. Finally, a hybrid load balancer eliminates the need to collect all load information on a single node by applying the NAMD centralized load balancer strategies independently to groups of 512 cores. The combination of SMP, memory optimization, parallel I/O, and hybrid load balancing now allows a simulation of 100 million atoms to run on a 16,384-node IBM BlueGene/P with only 2 GB of memory per node and to scale to all 224,076 cores of a Cray XT5 at ORNL.

Current performance studies targeting the Blue Waters platform are based on a single POWER7 node at NCSA and a single "drawer" at IBM, with performance results from the drawer still covered by a non-disclosure agreement with IBM. The single-node POWER7 performance results are excellent, with each POWER7 core providing 2.3 times the performance of a Cray XT5 2.6 GHz (Istanbul) Opteron core.

Based on our XT5 scaling results and relative POWER7 performance, and assuming improved scaling due to both software enhancements and a superior network, we anticipate being able to perform a simulation of 100 million atoms on 300K cores of Blue Waters at 5 ms per step. More accurate predictions will be possible after the installation of a significant fraction of the final machine in 2011. In the meantime, performance tuning will proceed with scaled-down million-atom simulations that replicate the communication properties of a 100M-atom simulation.

BTA UNIT: C

TITLE: Whole-cell Simulation of In Vivo Reaction Diffusion Processes

KEYWORDS: master equation, cell architecture, GPU

INVEST1: Zaida Luthey-Schulten
DEGREE1: Ph.D.
DEPT1: Department of Chemistry
NONHOST1:

INVEST2: Elijah Roberts
DEGREE2: Ph.D.
DEPT2: Department of Chemistry
NONHOST2:

INVEST3: John Stone
DEGREE3: M.S.
DEPT3: Beckman Institute
NONHOST3:

INVEST4: Wolfgang Baumeister
DEGREE4: Ph.D.
DEPT4: Department of Molecular Structural Biology
NONHOST4: Max Planck Institute of Biochemistry, Martinsreid, Germany

INVEST5: Julio Ortiz
DEGREE5: Ph.D.
DEPT5: Department of Molecular Structural Biology
NONHOST5: Max Planck Institute of Biochemistry, Martinsreid, Germany

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ABSTRACT: The Resource has begun development of a new software package for efficient simulation of the reaction-diffusion master equation, named "Lattice Microbes". Development is focused on optimizing the software for the simulation of whole-cell models including approximated *in vivo* crowding. Through the use of graphics processing units (GPUs) we have been able to extend simulation sizes and times to the scale of cells and cell cycles. The new software will allow computational biologists to take advantage of data regarding the cellular architecture now being collected from

experiments such as cryoelectron tomography (CET) and single-molecule, single-cell fluorescence. In collaboration with Julio Ortiz and Wolfgang Baumeister at the Max Planck Institute in Martinsreid, Resource researchers have used single-cell CET reconstructions as the basis for building a three-dimensional model of an *E. coli* cell. Using this model they studied the effect of spatial heterogeneity on gene expression in bacteria [105].

Current development efforts are focused on improving the performance of the software. In particular, Resource researchers are optimizing the code for execution on high performance computing clusters with multiple GPUs per node.

Resource Summary

BTA unit: (T)

NUMBER PUBLISHED -

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

NUMBER IN PRESS -

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

PUBLISHED:

Books:

Papers:

Abstracts:

IN PRESS:

Books:

Papers:

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BTA unit: (C)

NUMBER PUBLISHED -

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

NUMBER IN PRESS -

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

PUBLISHED:

Books:

Papers:

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IN PRESS:

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BTA unit: (S)

NUMBER PUBLISHED -

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

NUMBER IN PRESS -

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

PUBLISHED:

Books:

None.

Papers:

None.

Abstracts:

None.

IN PRESS:

Books:

None.

Papers:

None.

Abstracts:

Software Releases

BTA unit: (D)

NUMBER PUBLISHED -

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

NUMBER IN PRESS -

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

PUBLISHED:

Books:

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Advisory Board 2010
Summary Report

The Advisory Panel met October 17-18 in New York City. Members of the Panel are Angel E. Garcia (Rensselaer, Chair of the Panel), Richard Pastor (NIH), Jeffrey Skolnick (Georgia Tech), Dev Thirumalai (U Maryland), and Harel A. Weinstein (Cornell).

Introduction

Klaus Schulten

Resource director, Klaus Schulten, introduced the yearly meeting of the advisory board with a focus on preparation of the renewal proposal due in the fall of 2011. He stated that four cores are planned and described:

Molecular dynamics with NAMD Molecular analysis with VMD Structure solution with Molecular Dynamics Flexible Fitting (MDFF) Tools for Modeling of Membrane and Nanoengineering Processes

In addition, collaborations with intramural researchers and extramural researchers at US and European institutes will be suggested in a presentation.

Lastly, the key ideas for the areas training, service, dissemination, and management will be outlined.

The Resource director also posed a series of general questions to the board that rehire specific focus. In particular the questions: What is the value of the Resource for biomedical research? How does the Resource combine computing technology, software, and biomedical science? What new biomedical science does the Resource achieve and allow others to achieve? Is the Resource focus unique?

Service, Dissemination, Training, and Administration

Angela Weiss

The Resource provides user focused service in five different areas. The website serves as a portal to the Resource's software, publications, training material, and resources. Scientific software namely VMD and NAMD are a service the Resource provides to the scientific community. The Resource's world-class computational facility provides computational clusters, large networked disk storage, and graphical visualization facilities for biophysical research. In the past year the Resource has enjoyed an allocation of 42 million SUs of supercomputing time from TeraGrid and IACAT. The Resource's visitor program serves to provide onsite access to its computational facility, software, and hands-on training and consultation from the developers and researchers.

Additionally, the Resource offers seminars, workshops, consultations via mailing lists, and tutorials for its software giving the scientific community knowledge to leverage the capabilities of the group's software.

Training efforts at the Resource included two computational biophysics workshops, a workshop on graphical processing units (GPUs), and two collaborative workshops. The computational biophysics workshops were held at the Pittsburgh Supercomputing Center (PSC) (May 10-14, 2010) and the Scripps Research Institute (SRI) (July 12-16, 2010) and were populated by 30 and 33 scientists, respectively. The workshop format provided participants with conceptual lectures followed by hands-on tutorial experience with the Resource's VMD and NAMD software packages, and their application to scientific research. Both events received very positive evaluations, with 100% of those attending the PSC event indicating they gained new knowledge and insights, and 95% of those at the SRI event indicating a broader understanding of concepts and principles in computational and theoretical biophysics. The August 6-8, 2010 GPU workshop (attended by 19 scientists) provided participants with conceptual lectures on a variety of GPU- related subjects, such as programming and algorithm reviews, and the chance for in-depth discussions of their own projects. Evaluation results from participants are very positive, with 100% agreeing that the workshop broadened their understanding of concepts and principles in the field of GPU programming for molecular modeling. Collaborative workshops are those workshops utilizing Resource training materials, lecturers, or both in a workshop organized by outside groups. One event, held at the Universidad de Talca in Chile (November 23-26, 2009) utilized Resource tutorials across all days of the workshop. Another event, the CryoEM Map Workshop at the National Center for Macromolecular Imaging at the University of Houston (January 14-17, 2010), included a day of lectures and tutorials by the Resource members, with the tutorial session incorporating two new tutorials. Three new tutorials (molecular dynamics flexible fitting, structure check, and modeling nanopores) were released over the last 12 months, and tutorials used in workshops received updates. Online versions of the tutorials and case studies continued to draw heavy web traffic, with over 90,000 views of tutorials (counting html and PDF files) and over 9,000 views of case studies. The Resource will conduct two more hands-on workshops in November 2010, and is currently organizing three more such workshops in March, May, and October 2011. Three more tutorials, on quantum chemistry visualization, the timeline trajectory tool for VMD, and electrostatics maps and ion conduction are targeted for release in the next twelve months.

Dissemination at the Resource is achieved by pursuing all available traditional (e.g., journal articles) and electronic (e.g., websites) channels, and by experimenting with media options. Over the last reporting period, the Resource produced 43 publications (with six more in press and seven submitted), and processed over 600 reprint requests. In outreach activities, the Resource responded to 53 requests to use its images and movies, was part of 45 stories from media outlets, and had thousands of views of its YouTube gallery. The Resource web site continued to be the Resource's most critical dissemination tool, with over 800,000 unique visitors over the past 12 months, resulting in 3.2 terabytes of

information transfer. Registrations via the web site grew to over 40,700 for NAMD, over 168,000 for VMD, and over 4,500 for BioCoRE. Further, over 10,000 web sites link into the Resource domain, with 1,000 sites linking to the main page of the web site. The future of dissemination at the Resource will include continuation of successful strategies, and experimentation with new options (e.g., Facebook, blog efforts), with success of a particular effort based on its content and maintenance requirements, and its estimated utility to the biomedical community.

The Resource also started outreach programs aimed at school age children (elementary through high school) to interest these students in science and technology. Programs reached from formal teaching that is part of the school curriculum to less formal summer camps that were used to showcase the Resource's scientific endeavors. Further activities are in the planning state.

The Resource in the past year has been focusing its efforts in preparing and augmenting its computational facility for Petascale computing and millisecond simulations. The Petascale Molecular Dynamics Data Processing System grant from the NIH has greatly helped the Resource in moving towards this goal. In the past year, the Resource has more than doubled its shared disk capacity to 560 Terabytes providing room for the large simulations Petascale computing will bring. New application servers have been purchased and are being deployed to handle the increased workload and computer traffic Petascale computing will require. The Resource has greatly bolstered its computational resources with the acquisition of large memory and GPU (Graphical Processing Unit) accelerated analysis machines. These machines allow Resource scientists to analyze large and complex simulations faster, more efficiently, and with less physical computers than before. A new, high-resolution 3D projection facility has been deployed by the Resource in the past year allowing high performance and detailed displays of complex models and Petascale simulations. Additionally, the Resource has greatly increased the computational power available to each researcher at their desk with new graphical workstations and high-resolution displays. The Resource remains very committed in preparing itself for upcoming Petascale computing and millisecond simulations.

All these activities (particularly mailing lists, webpage and tutorials) consume much time and effort that could be put into development. About three full positions spread over several staff members are dedicated to these kinds of activities. To ease this problem the Resource hired two more programmers this year that will help further developmental efforts.

The advisory panel is very impressed with the organization, breath and reach of the dissemination and training. The panel has two minor suggestions:

1. That the Resource collects measures about the reach and impact of the training

programs. These measures could include:

(a) Number of publications by participants of the training workshops that made use of the VMD, NAMD and other programs and tutorials provided by the Resource;

(b) Academic ranking of participants (students, graduate students, PD, etc.)

(c) Research subject. Specify number of participants from experimental or theoretical; biological sciences vs. physical sciences, etc.

2. Create tutorials adding who are these addressing and what is being done. This could help reach experimental groups.

Core I: NAMD

Laxmikant Kal and Jim Phillips

NAMD is a scalable parallel program for the molecular dynamics simulation of biomolecular systems. Specific aims for NAMD are to extend simulation timescale and size, accelerate performance using emerging technologies, provide new simulation methods, and improve the scientific productivity of biomedical researchers. NAMD is mature software with over 40,000 users, of which over 10,000 have downloaded more than one version, and about 18% of the user base is funded by NIH. Four versions of NAMD were released in the past year: 2.7b2, released in November, had 5900 users in 7 months; 2.7b3, released in July, had 2000 users in 2 months; 2.7b4, released in September, had 900 users in 1 month; and 2.7 final, released in October, has over 300 users in its first week. Over 3000 users have downloaded nightly builds since March to access new features and bug fixes. NAMD runs on a wide range of hardware, from supercomputers to Linux clusters and is even well-supported on desktops and laptops under all major operating systems and can take advantage of both shared-memory and network-based parallelism.

NAMD is based on the Charm++ parallel programming system developed in the group of co-PI Kale, in which the programmer specifies parallelism that is then mapped by the runtime system onto the parallel machine. As a result, the NAMD user experience is the same on all platforms with no change needed in input, output, or configuration files to enable any simulation to be run on any number of processors. Continuous effort is required to tune and adapt NAMD and Charm++ to new platforms and to improve performance and usability. For example, NAMD 2.7b2 introduced native Charm++ InfiniBand support, allowing the Resource to ship portable binaries using this increasingly affordable and necessary interconnect, eliminating the need for many users to compile NAMD themselves. This was followed in 2.7b3 by the ability to launch non-MPI InfiniBand binaries using the mpiexec program already present and supported on most clusters,

thus eliminating the complex task of writing scripts to deal with whatever queuing system is present on a cluster.

The NSF petascale Blue Waters machine, to be operational at Illinois in 2011, is a focus of NAMD development. A 100-million atom NAMD simulation is an acceptance test for the machine, and some funding is provided by NCSA for this purpose. The Resource has also received a preliminary allocation on the machine for simulations of the chromatophore and other systems. The goals are to simulate 10M atoms at a rate of 10ns/day, 1M at 50ns/day, and 100K at 100ns/day.

The resource developed new techniques to support simulations of large molecular systems during the past year. The resource developed an atom-signature based representation that allowed the memory on each node to be reduced, in conjunction with new file formats. Further reductions in memory were obtained by parallel input/output strategies. These strategies also reduced the amount of time required at startup.

Since output happens periodically, it was important to reduce the time required for it, in addition to the memory requirements. A parallel output scheme was implemented that achieves the memory reduction. The time-reduction initially proved elusive because parallel file systems on many parallel machines were not adequate for the task. A workaround was developed, that provided surprisingly good performance, because output time could be overlapped with simulation timesteps. The resource plans to explore additional ways of reducing the time and memory requirement for output.

Performance scaling studies of a 12 million atom water bubble (without any special water-specific optimizations) were carried out on BlueGene/P machine up to 32,000 processors, and on Cray XT5 machine to over 15,000 processors. The performance on BlueGene showed almost- perfect efficiency, whereas on Cray the efficiency drops beyond 7,000 processors, although performance continues to improve. Extensive scaling studies for systems between 10-25 million atoms are planned for the pre-proposal phase.

A hierarchical load balancer has also been integrated with NAMD and both shared-memory and parallel I/O are being used in production simulations of 10-20 million atoms and planned for release in NAMD 2.8 in January. Full support for 100-million atom acceptance test running on Blue Waters is planned for NAMD 2.9 in August.

Another aim for NAMD is to make available new simulation methods, developed at the Resource or outside. We have worked closely with Benoit Roux to implement the Drude polarizability model, first released in NAMD 2.7b3 and updated in 2.7, in order to support rapid development of the force field parameters. Other new released capabilities include tabulated nonbonded potentials, the TIP4-P water model, Random Acceleration MD, and the Lowe-Andersen thermostat. A Generalized Born (OBC) implicit solvent model, new restraint methods for MD Flexible Fitting, and accelerated MD methods are now

being tested and will be released in NAMD 2.8 in January. Car-Parrinello QM/MM simulation capability linking NAMD to the Charm++-based OpenAtom plane wave QM code is now being completed and will be released in NAMD 2.9 in August.

Production simulations with NAMD on the GPU-accelerated NCSA Lincoln cluster have been underway for much of the year based on NAMD 2.7b2. Later releases have improved GPU acceleration through tuning for the new NVIDIA Fermi processors and the use of pairlists. GPU- accelerated NAMD supports most simulations, but not alchemical free energy perturbation or other methods that modify nonbonded interactions. Each GPU increases performance by roughly the same as 12 CPU cores, with the unaccelerated PME reciprocal sum being the primary bottleneck. In the coming year the Resource will collaborate with NVIDIA to further improve performance for NAMD 2.9 to be released in August.

Resource plans for the next proposal period will attack simulation challenges in the areas of accuracy, timescale, sampling, and performance. Simulation accuracy will be enhanced through polarizable force fields, constant pH simulations, long-range dispersion forces, and QM/MM simulation. Timescale will be addressed through collaboration with developers of coarse grained models, performance enhancement of implicit solvent to support Core 3 MDFF development, and implementation of Brownian dynamics to support Core 4 membrane transport studies. Sampling improvement will build and extend the NAMD 2.7 free energy features, support accelerated sampling methods, and support replica-based methods directly in Charm++ rather than relying on scripting.

Performance will be addressed through finer-grained and more tightly coupled GPU acceleration and continued scalability improvements to harness both increasingly common petascale and next- generation exascale machines in close collaboration with both the Charm++ developers and NVIDIA. The resource hopes to carry out multi-million atom simulations at the rate of a microsecond-a-day by the end of the performance period in 2017.

The advisory panel recognizes NAMD as a state of the art, mature software that has no equal in the biosciences community. The developer's effort to maintain the program and to take advantage of new technologies is outstanding. The addition of atomic polarizabilities and Car-Parrinello QM/MM methods, in a scalable software will keep NAMD at the forefront in the field of biomolecular simulations.

Core II: VMD

Zaida Luthey-Schulten and John Stone

VMD 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.

The most recent release of VMD, version 1.8.7, was released in August 2009. Since the VMD 1.8.7 release, over 43,300 unique users have registered and downloaded the software. Of the registered users of version 1.8.7, over 7,700 are NIH-funded researchers, representing about 18of the total VMD user community.

VMD runs on all major operating systems and supports computers ranging from laptops to supercomputers. VMD takes advantage of advanced hardware technologies including stereoscopic displays, six-degree-of-freedom input devices with haptic feedback, multi-processor and clustered rendering systems, OpenGL, programmable shading, 64-bit addressing, multi-core processors, and GPU-accelerated computation supporting both the CUDA and OpenCL APIs for GPU and heterogeneous computing.

VMD continues to be a successful and widely used molecular visualization and analysis program. VMD excels at visualizing large all-atom structures (over 100 million atoms) and long time scale molecular dynamics trajectories. While originally developed as a companion program for the Resource's program NAMD to visualize molecular dynamics trajectories, VMD's unique modular design allows the incorporation of plugins that extend its capabilities into other areas such as bioinformatics [MS1-9] coarse grained representations of subcellular processes and bionanodevices, and most recently for quantum chemistry and lattice cell simulations [CellGPU1- 2]. The latest version of the MultiSeq evolutionary analysis plugin adds improved support for nucleic acid sequences/structures and improves performance over previous versions. Multiseq has been run over 40,684 times from 5,705 unique machines, as measured by accesses to the web- based Multiseq metadata repository hosted by the Resource.

On-going and Future Directions in VMDs Technological Development: New features developed for MultiSeq stem directly from scientific applications, and some are still in the process of being implemented as GUI interfaces into VMD. They include mutual information and signature analysis of RNA, sequence analysis of large RNA databases (Greengenes), RaxML phylogenetic trees, and scripting of genomic context and functional annotation. MultiSeq now supports the popular software package MAFFT for multiple sequence alignments, while maintaining support for ClustalW package already available in prior versions. MAFFT enables Multiseq to perform multiple sequences alignments on very large collections of sequences with high performance. As the additional features are integrated into MultiSeq:VMD, the tutorials [TUT1-3] are continually updated and revised.

The Network Viewer plugin [TUT4]for the analysis of dynamical networks throughout the entire ribosome will allow more rapid correlation with experimental data on its functional motions. It has already been tested on the other RNA:protein complexes involved in translation through collaborations with leading x-ray crystallographers and biochemists and through recent NIH and NSF sponsored workshops.

Integration of cell architecture from 3D reconstructions of cryoelectron tomograms (CET) with proteomics data allows us to now analysis biochemical processes in whole cell simulations using realistic models of in vivo molecular crowding. The simulations make use of the GPU technology and represent challenges to VMDs abilities to visualize dynamics of coarse-grained components and open systems. The reaction diffusion master equations describing the processes, which include the effects of spatial heterogeneity, have been and will continue to be refined in collaboration with the NIH Resource staff.

Recently, the Resource has adapted VMD for batch mode parallel execution on clusters and supercomputers using the widely-supported Message Passing Interface (MPI) parallel communication standard. Although still in a prototype stage, this new feature makes it possible for researchers to run computationally demanding or memory-intensive trajectory and bioinformatics analysis calculations relatively easily, and much faster than would otherwise be possible using a conventional desktop computer.

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 VMD scripting commands.

The MPI-based parallel VMD implementation maintains VMD's existing support for other technologies such as multi-core CPUs, and GPU acceleration, while enabling hundreds of so- called "nodes", individual computers comprising the cluster, can be collectively harnessed to analyze large size and long timescale simulation trajectories. These technological advances will provide the functionality needed to support petascale simulations on upcoming supercomputing facilities such as the NSF Blue Waters system.

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.

In the past year, VMD has been improved with many new features, with an emphasis on building infrastructure for efficient use of graphics processing units (GPUs) for acceleration of computationally demanding visualization and analysis tasks on desktop workstations. The software implementations in VMD are primarily based on NVIDIA's CUDA GPU programming toolkit, but several have also been adapted to OpenCL. The Resource has implemented new GPU accelerated algorithms for computing electrostatic potential maps of non-periodic and periodic systems (speedup factor of up to 44x), for

the implicit ligand sampling algorithm that computes gas migration pathways in proteins (speedup factor of up to 30x), for interactive animation of quantum chemistry simulation trajectories (speedup factor of up to 120x), and calculation of radial pair distribution functions (speedup factor of up to 92x).

The Resource has made significant progress in developing internal software infrastructure in VMD to enable GPU accelerated algorithms to use multiple GPUs in parallel, thereby further increasing the peak performance achievable in a desktop computer. The Resource has implemented prototype multi-GPU versions of the quantum chemistry visualization (speedup factor of up to 412x) and radial pair distribution function (speedup factor of up to 360x) algorithms, and these will be part of the upcoming VMD 1.8.8 release. The Resource plans to adapt the other existing VMD GPU algorithms for multi-GPU usage in the coming months.

The Resource is currently developing new GPU algorithms for molecular dynamics trajectory visualization analysis, a broader range of quantum chemistry visualization and analysis capabilities, and for high performance molecular surface and secondary structure display.

The GPU algorithms developed by the Resource have been published in a sequence of 14 papers and 3 book chapters since 2007. The ones alone for 2010 are listed in:
`http://www.ks.uiuc.edu/Research/gpu`

Resource staff has been actively involved in disseminating GPU computing research and teaching GPU programming techniques at many recent conferences and workshops:
`http://www.ks.uiuc.edu/Research/gpu/#presentations`
`http://www.ks.uiuc.edu/Research/gpu/#classes`

In August, the Resource hosted a 3-day hands-on GPU programming workshop for molecular modeling applications, attended by 19 researchers from research institutions and corporations across the United States:
`http://www.ks.uiuc.edu/Training/Workshop/GPU_Aug2010/`

The performance benefits of GPUs, combined with recent advances in commodity six-degree-of- freedom input devices and low-cost stereoscopic display are creating a unique opportunity to make immersive visualization and interactive modeling technologies available to a much broader range of molecular scientists than was previously possible.

The Resource has recently adapted VMD for use with a variety of low-cost three- and six-degree- of-freedom input devices, including those with haptic feedback, such as the Novint Falcon. The Resource has recently developed an early prototype implementation of VMD enabling smart- phones to be used as wireless input devices for VMD. The Resource expects to develop this technology further as smart-phone become more sophisticated, adding gyroscopes and other high- fidelity six-degree-of-freedom motion input sensors.

2010 TUTORIALS FOR MULTI-SEQ/VMD AND NETWORK PLUGIN

1. Evolution of Translation: EF-Tu:tRNA, (2009/revised 2010) Magis A., Chen K., Eargle J., Roberts E., and Luthey-Schulten Z.
   `http://www.scs.uiuc.edu/schulten/tutorials/ef-tu`

2. Evolution of Translation: The Ribosome, (2009/in revision 2010), Magis A., Chen K., Mathew D., Eargle J., and Luthey-Schulten Z.
   `http://www.scs.uiuc.edu/schulten/tutorials/ribosome`

3. Evolution of Translation: Class-I Aminoacyl-tRNA Synthetases, (2009/in revision 2010) Li L., Sethi A., and Luthey-Schulten Z.
   `http://www.scs.uiuc.edu/schulten/tutorials/evolution`

4. Dynamical Network View: (2010/in revision and implementation into VMD extensions) Eargle, J., Li, L. Luthey-Schulten, Z.

The advisory board recognizes VMD as a state of the art graphics visualization program that is widely used by the biosciences community. Recent developments of the program integrate sequence analysis and network analysis, with structure visualization and evolutionary analysis. In addition, plugins and new software has been developed to include pathway analysis into MultiSeq and to visualize cell simulations. The panel has recommended that i) VMD should also read MCell data. ii) The cell simulations software opens the opportunity to develop a new tool; iii) The Resource should explore how to collaborate on network analysis with the BIOMAPS project.

Core III: Structure solution with Molecular Dynamics Flexible Fitting (MDFF)
Klaus Schulten

Resource director Schulten presented the planned third core, focused on multi-modal structure solution methodologies. In a first part of the presentation, Schulten explained the molecular dynamics flexible fitting (MDFF) method that combines crystallographic and electron microscopy data to solve structures where neither method alone works. The method was demonstrated dramatically for the case of the ribosome and twelve publications that introduced and applied the method were listed, including PNAS and Science papers. Impressive was that the method stood the test in resolving the first structure, that of a ribosome - kirromycin complex, in which the ribosome is stalled in a state triggering EF-TU GTP hydrolysis. This structure was solved later by Nobel laureate V. Ramakrishnan, and both structures were found to agree essentially, with a key difference later shown to be due to different tRNAs used. A dramatic application that was most recently completed shows the ribosome in a state of docking to SecY embedded in a lipid bilayer with a nascent protein seen to weave itself into the membrane.

The Resource showed off a series of pre-proposal goals that it seeks to achieve before June 2011 to strengthen its proposed new Core 3 further, in particular, to improve and accelerate the Resource software that executes the needed NAMD computations. The Resource has hired recently a new, young programmer, Ryan McGreevy, who will focus his work mainly on MDFF development and has achieved already impressive progress after just a few months. McGreevy promises to play the same role for MDFF that Resource staff, Stone and Phillips, play for VMD and NAMD, respectively. The goals include pushing ahead and publishing ongoing MDFF applications on the ratcheting motion of the ribosome, on genetic decoding inside the ribosome, on nascent protein behavior in the ribosome exit channel and beyond, and on the entry mechanism of polio virus. The pre-proposal goals on the methodological side include development of a test set for evaluation and validation of MDFF structures, use of local cross correlation as a driving for in MDFF refinement, development of interactive MDFF through use of GPU computing, the option of symmetry restraints, e.g., for helically arranged structures, and MDFF using implicit solvent NAMD. The latter variant of scalable NAMD has been recently achieved by the Resource and deserves much praise.

Schulten finally discussed the long range goals for a new Core 3 that include the acceleration of MDFF through GPU computing, speeding up the grid-based formulation of EM map based forces guiding MDFF refinement and the systematic use of local cross correlation for this purpose. The scope of MDFF will be widened to not only combine crystallographic and cryo-EM data, but also other experimental data stemming from NMR (NOE intensities, long-range NOE, J-coupling constants, hydrogen bonds), optical spectra (smFRET), or biochemistry (cross-linking). The Resource seeks to also develop descriptors for quality of fitting, use of hierarchies of restraints, and to automate fitting protocols for very large macromolecules. Lastly, the MDFF method will be extended to low resolution X-ray crystallography.

The panel finds the MDFF tool very useful and unique. A concern with this tool is the limited reach, since there are not many problems that will require using this tool.

Core IV: Tools for modeling and simulation of membrane proteins and biotechnological applications

Emad Tajkhorshid and Aleksei Aksimentiev

This core is a new core focusing on developing and implementing tools that allow for an efficient and user-friendly application of modeling and simulation methodologies to studying molecular phenomena related to membrane proteins and biotechnological applications. The core is developed owing to the long tradition of the Resource and its faculty in studying membrane proteins and, in more recent years, biotechnology. The plan for this new core was outlined jointly by Emad Tajkhorshid and Aleksei Aksimentiev who will lead the effort and work on various tools. In the membrane protein part of the core,

the emphasis will be on methods that will enable one to study large-scale protein conformational changes specifically in membrane proteins, and on developing new models for membranes that will allow a significantly improved degree of sampling of protein-lipid interactions. Several promising applications of the new model in various peripheral proteins, e.g., coagulation proteins and talin/integrin was briefly described by E. Tajkhorshid. Many of the tools developed in this part will be also useful in studying other classes of biomolecular systems.

The plans and progress for biotechnological tools were presented by A. Aksimentiev. Building on the pioneering work that demonstrated utility of all-atom MD simulations in predicting transport properties of ion channels and nanopores, this part aims to dramatically increase computational efficiency of the transport models while preserving their atomic precision. Among recent successes are implementation of Lowe-Andersen thermostat in NAMD, a thermostat that conserves momentum and thus is better suited for transport simulations, support for multi-resolution grid forces in NAMD, and preliminary development work that bridged the computational efficiency of the Brownian Dynamics (BD) method with the accuracy of the all-atom approach. Immediate development goals are directed toward making a prototype tool for mapping a membrane channel's three-dimensional potential of mean force (PMF) and local diffusivity, and dissemination of the tools through a comprehensive tutorial. Future plans are to integrate 3D-PMF/BD simulations within VMD/NAMD and expand the BD implementation in NAMD to include hydrodynamic interactions, support BD models of polymers and globular particle dynamics.

The work presented by Aksimentiev addresses the use and development of the Resource tools to biotechnology and biomaterials. This aspect is unique and important. The tool to built membrane systems needs further development and should probably be included as part of VMD. The panel has suggested that MDFF, the cell modeling and the biotechnology tools be combined as an application core.

Collaborations

Klaus Schulten

Resource director Schulten presented the collaborations planned for the initial phase of the next funding period, 2012-2017. The collaborations, as he stated, should be both exciting biomedical research problems as well as technological challenges in the area of the Resource, e.g., involve large scale (million atoms or more), long time scale (many microseconds) MD, or new analysis methodologies as they arise for large amounts of trajectory data.

The collaborations were grouped by Schulten according to collaborations with intramural research groups, extramural US research groups, and extramural European research groups. 17 candidate collaborations were presented, a number that will be reduced even-

tually to 10-12. Schulten emphasized that the inclusion of European groups is essential as they are of extremely high quality, not only representing great science, but also outstanding technological challenges.

Schulten is co-founder and co-director of a new NSF funded Physics Frontier Center "Center for the Physics of Living Cells" (CPLC) that is involved in spectacular research carried out by University of Illinois at Urbana-Champaign (UIUC) faculty from Physics, Chemistry, Biochemistry, and Molecular and Cell Biology as well as Bioengineering. The collaborations with the Resource are all with CPLC faculty. A collaboration with Chemistry professor Martin Gruebele studies pressure induced in vitro protein fielding as well as in vivo protein folding; a collaboration with Physics professor Paul Selvin resolves key structural intermediates in myosin VI motor function, a collaboration with Physics professor Taekjip Ha investigates the physical mechanisms of helicases, a collaboration with Physics professor Yann Chempla studies the Telk- DNA complex, a collaboration with Biochemistry professor Steve Sligar studies the use of nanodiscs for membrane associated protein function, and a collaboration with a broad faculty consortium seeks to study the membrane activation of coagulation factors.

The Resource enjoys six strong ongoing and recently initiated collaborations with extramural research groups in the US that are considered for the renewal proposal. The research groups are located at Columbia U. (Frank, Gonzales: ribosome structure and mechanism), at the U. of Chicago, the center of a new glue grant on membrane proteins (Roux, Perozo: polarizable force fields and potassium channel gating), at Harvard U. (Hogle: polio virus infection) and at the U. Washington and U. Alabama (Gundlach and Niederweis: DNA sequencing using MspA).

Finally, the Resource seeks to continue engagement into fruitful long range collaborations with European groups: Gaub, Munich, epigenetic mechanisms; Beckmann, Munich, nascent proteins in the ribosome; Scheuring, Paris, photosynthetic membrane; Baumeister, Munich, Whole cell imaging and modeling; Lim, Basel, nuclear pore complex gating.

The Advisory Panel is impressed by the breath and extent of the collaborations of the Resource scientists with top experimentalist around the world. The Resource has a strong record of fruitful collaborations with an impressive number of publications. The past collaborations excelled, both, in regard to the quality of science, as well as in regard to the provision of new technological solutions. This bodes well for the selection and completion of new collaborative projects.

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 Resource investigators. Drs. Schulten and Aksimentiev have ap-

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

†`http://www.uiuc.edu/`

pointments in the Department of Physics; Drs. Schulten, Luthey-Schulten and Tajkhorshid 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 four software developers, eight postdoctoral associates, 15 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, providing 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:

- 29,455 additional users of VMD
- 7,826 additional users 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/`

- 590 additional registered users of BioCoRE
- 4,455 VMD emails, 624 NAMD emails, and 98 BioCoRE chats and emails were exchanged in user support
- over 812,000 unique visitors to Resource software web site
- 5,496 citations of the VMD source paper; 2,503 citations of the NAMD source papers
- 25 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 185,042 users as of May 2011 (an increase of 29,455 or +19% since April 2010), with 42,088 of those repeat users (i.e., they have downloaded more than one version of VMD), and 18.5% of all registered users indicating NIH funding. The current version of VMD, VMD 1.9, has 8,088 registered users since its release in March 2011, with 1,487 or 18% of users indicating they are NIH funded users.

NAMD has been downloaded by 44,950 users (as of May 2011) (an increase of 7,826 or +21% since April 2010), of whom 11,921 or 26.5% are returning users. 7,937 (18%) of NAMD users are NIH funded. The current version of NAMD, version 2.7 released in October 2010, has 4,719 registered users, with 866 or (18%) of users indicating NIH funding. The new NAMD beta, version 2.8b1, has 1304 registered users since its release in March 2011.

BioCoRE has 4,858 registered users (an increase of 590, or +19% in the past year), involved in 613 projects (compared to 585 a year ago). A total of 232 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 2010-2011 include amongst other features:

- VMD has been adapted to run on HPC clusters and supercomputers, enabling faster processing of complex simulation setup and analysis jobs using tens or hundreds of nodes in parallel. User-developed analysis scripts can now be easily adapted for parallel execution. Most recently the parallel analysis features of VMD have been implemented for the new "Blue Waters" supercomputer expected to become available in late 2011.

- VMD makes use of GPU-accelerated algorithms to achieve high performance for computationally demanding tasks, such as calculation of radial distribution functions, computing 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 faster rendering for scenes with ambient occlusion lighting, often used 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. The latest release of VMD adds support for the X3D scene format enabling molecular graphics to be interactively displayed on the web and loaded into other tools. The latest version of VMD includes improvements to allow scene files to be saved in the Wavefront scene file format, enabling VMD molecular graphics to be loaded into professional rendering and animation packages such as Autodesk Maya.

- 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, and the new carbon nanostructure builder tool. The new version of Molefacture includes an updated interface for antechamber, providing users with improved auto-typing and semiempirical geometry optimizations for fast structure cleanup. Finally, a new graphical interface greatly simplifies the process of setting up and analyzing free energy perturbation (FEP) calculations performed in NAMD.

Scope of VMD User Support:

- 4,455 e-mail exchanges in response to user inquiries sent to the vmd@ks.uiuc.edu e-mail address
- 1,090 subscribers to the VMD-L mailing list, with 18,014 total postings, and 2,224 postings for the April 2010 - May 2011 period
- Local face-to-face support has been provided

There are currently 749 non-Resource users with access to the VMD source code repository, with 164 such users added in the last year.

Sites with Links to the VMD Site (via Yahoo! site search, April 2011): 4,327 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 2010-2011 include among other features:

- Generalized Born implicit solvent model
- Accelerated molecular dynamics method
- MARTINI residue-based coarse-grain forcefield
- Non-uniform grids in grid forces
- New symmetry and domain restraints
- Force output and trajectory files
- Measurement-based grain-size adjustment in load balancer
- Type-pair specific nonbonded parameters with GPU acceleration
- Port to Microsoft Windows HPC Server

NAMD Availability in Supercomputer Centers:

- 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 63 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"
- 870 subscribers to the NAMD-L mailing list, with 14,247 total postings, and 2,312 postings for the April 2010 - May 2011 period.
- Over 624 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 562 users with access to the NAMD source code repository, with 31 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 12,527 times by 5094 users since their introduction in March 2009.

Sites with Links to NAMD site (via Yahoo! site search, April 2011): 1,940 links

BioCoRE User Support:

- 23 emails issued to/from biocore@ks.uiuc.edu from April 2010 - May 2011
- 98 chat messages sent to the BioCoRE public help project from April 2010 - May 2011 within BioCoRE itself.

Sites with Links to BioCoRE site (via Yahoo! site search, May 2011): 157 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 and NAMD source papers are provided below.

List of papers citing VMD: A literature search in the ISI Web of Science citation database in May 2011 yielded 5,496 published journal articles, papers, or books citing the VMD origin paper [1]. Below are 25 recent citations:

- Tang, Grace W. and Altman, Russ B. (2011). Remote Thioredoxin Recognition Using Evolutionary Conservation and Structural Dynamics. *Structure*, 19(4), 461-470.

- Li, Zhenlong and Dormidontova, Elena E. (2011). Equilibrium chain exchange kinetics in block copolymer micelle solutions by dissipative particle dynamics simulations. *Soft Matter*, 7(9), 4179-4188.

- Ponomarev, Sergei Y. and Audie, Joseph. (2011). Computational prediction and analysis of the DR6-NAPP interaction. *Proteins-Strucutre Function and Bioinformatics*, 79(5), 1376-1395.

- Simpson, Lisa M. and Wall, Ian D. and Blaney, Frank E. and Reynolds, Christopher A. (2011). Modeling GPCR active state conformations: The beta(2)-adrenergic receptor. *Proteins-Strucutre Function and Bioinformatics*, 79(5), 1441-1457.

- Sander, Tommy and Frolund, Bente and Bruun, Anne Techau and Ivanov, Ivaylo and McCammon, James Andrew and Balle, Thomas. (2011). New insights into the GABA(A) receptor structure and orthosteric ligand binding: Receptor modeling guided by experimental data. *Proteins-Strucutre Function and Bioinformatics*, 79(5), 1458-1477.

- Gao, Mu and Skolnick, Jeffrey. (2011). New benchmark metrics for protein-protein docking methods. *Proteins-Strucutre Function and Bioinformatics*, 79(5), 1623-1634.

- Martinez, Leandro and Malliavin, Therese E. and Blondel, Arnaud. (2011). Mechanism of reactant and product dissociation from the anthrax edema factor: A locally enhanced sampling and steered molecular dynamics study. *Proteins-Strucutre Function and Bioinformatics*, 79(5), 1649-1661.

- Sampathkumar, Parthasarathy and Gheyi, Tarun and Miller, Stacy A. and Bain, Kevin T. and Dickey, Mark and Bonanno, Jeffrey B. and Kim, Seung Joong and Phillips, Jeremy and Pieper, Ursula and Fernandez-Martinez, Javier and Franke,

Josef D. and Martel, Anne and Tsuruta, Hiro and Atwell, Shane and Thompson, Devon A. and Emtage, J. Spencer and Wasserman, Stephen R. and Rout, Michael P. and Sali, Andrej and Sauder, J. Michael and Burley, Stephen K. (2011). Structure of the C-terminal domain of Saccharomyces cerevisiae Nup133, a component of the nuclear pore complex. *Proteins-Strucutre Function and Bioinformatics*, 79(5), 1672-1677.

- Bellesia, Giovanni and Jewett, Andrew I. and Shea, Joan-Emma. (2011). Relative stability of de novo four-helix bundle proteins: Insights from coarse grained molecular simulations. *Protein Science*, 20(5), 818-826.

- Rupp, Bernd and Guenther, Sebastian and Makhmoor, Talat and Schlundt, Andreas and Dickhaut, Katharina and Gupta, Shashank and Choudhary, Iqbal and Wiesmueller, Karl-Heinz and Jung, Guenther and Freund, Christian and Falk, Kirsten and Roetzschke, Olaf and Kuehne, Ronald. (2011). Characterization of Structural Features Controlling the Receptiveness of Empty Class II MHC Molecules. *PLOS One*, 6(4).

- Sayle, Thi X. T. and Inkson, Beverley J. and Karakoti, Ajay and Kumar, Amit and Molinari, Marco and Moebus, Guenter and Parker, Stephen C. and Seal, Sudipta and Sayle, Dean C. (2011). Mechanical properties of ceria nanorods and nanochains; the effect of dislocations, grain-boundaries and oriented attachment. *Nanoscale*, 3(4), 1823-1837.

- Chan, Henry and Kral, Petr. (2011). Self-standing nanoparticle membranes and capsules. *Nanoscale*, 3(4), 1881-1886.

- Freed, Alexander S. and Cramer, Steven M. (2011). Protein-Surface Interaction Maps for Ion-Exchange Chromatography. *Langmuir*, 27(7), 3561-3568.

- Manna, Moutusi and Mukhopadhyay, Chaitali. (2011). Molecular Dynamics Simulations of the Interactions of Kinin Peptides with an Anionic POPG Bilayer. *Langmuir*, 27(7), 3713-3722.

- Azenha, Manuel and Szefczyk, Borys and Loureiro, Dianne and Kathirvel, Porkodi and Cordeiro, M. Natalia D. S. and Fernando-Silva, Antonio. (2011). Molecular Dynamics Simulations of Pregelification Mixtures for the Production of Imprinted Xerogels. *Langmuir*, 27(8), 5062-5070.

- Curutchet, Carles and Kongsted, Jacob and Munoz-Losa, Aurora and Hossein-Nejad, Hoda and Scholes, Gregory D. and Mennucci, Benedetta. (2011). Photosynthetic Light-Harvesting Is Tuned by the Heterogeneous Polarizable Environment of the Protein. *Journal of the American Chemical Society*, 133(9), 3078-3084.

- Beckham, Gregg T. and Crowley, Michael F. (2011). Examination of the alpha-Chitin Structure and Decrystallization Thermodynamics at the Nanoscale. *Journal of Physical Chemistry B*, 115(15), 4516-4522.

- Lu, Pinyi and Bevan, David R. and Lewis, Stephanie N. and Hontecillas, Raquel and Bassaganya-Riera, Josep. (2011). Molecular modeling of lanthionine synthetase component C-like protein 2: a potential target for the discovery of novel type 2 diabetes prophylactics and therapeutics. *Journal of Molecular Modeling*, 17(3), 543-553.

- Li, Li and Yu, Long and Huang, Qiang. (2011). Molecular trigger for pre-transfer editing pathway in Valyl-tRNA synthetase: A molecular dynamics simulation study. *Journal of Molecular Modeling*, 17(3), 555-564.

- Ohkubo, Takahiro and Kidena, Koh and Takimoto, Naohiko and Ohira, Akihiro. (2011). Molecular dynamics simulations of Nafion and sulfonated polyether sulfone membranes. I. Effect of hydration on aqueous phase structure. *Journal of Molecular Modeling*, 17(4), 739-755.

- Purohit, Rituraj and Rajendran, Vidya and Sethumadhavan, Rao. (2011). Relationship between mutation of serine residue at 315th position in M. tuberculosis catalase-peroxidase enzyme and Isoniazid susceptibility: An in silico analysis. *Journal of Molecular Modeling*, 17(4), 869-877.

- Levine, Benjamin G. and Stone, John E. and Kohlmeyer, Axel. (2011). Fast analysis of molecular dynamics trajectories with graphics processing units-Radial distribution function histogramming. *Journal of Computational Physics*, 230(9), 3556-3569.

- Berski, Slawomir and Latajka, Zdzislaw and Gordon, Agnieszka J. (2011). Electron Localization Function and Electron Localizability Indicator Applied to Study the Bonding in the Peroxynitrous Acid HOONO. *Journal of Computational Chemistry*, 32(8), 1528-1540.

- Artemova, Svetlana and Grudinin, Sergei and Redon, Stephane. (2011). Fast Construction of Assembly Trees for Molecular Graphs. *Journal of Computational Chemistry*, 32(8), 1589-1598.

- Jin, Lin and Auerbach, Scott M. and Monson, Peter A. (2011). Modeling three-dimensional network formation with an atomic lattice model: Application to silicic acid polymerization. *Journal of Chemical Physics*, 134(13).

List of papers citing NAMD: A literature search in the ISI Web of Science citation database in May 2011 yielded 2,503 published journal articles, papers, or books citing the current [2] or prior [3] NAMD origin papers. Below are 25 recent cites:

- Darian, Eva and Guvench, Olgun and Yu, Bing and Qu, Cheng-Kui and MacKerell, Jr., Alexander D. (2011). Structural mechanism associated with domain opening in gain-of-function mutations in SHP2 phosphatase. *Proteins-Structure Function and Bioinformatics*, 79(5), 1573-1588.

- Martinez, Leandro and Malliavin, Therese E. and Blondel, Arnaud. (2011). Mechanism of reactant and product dissociation from the anthrax edema factor: A locally enhanced sampling and steered molecular dynamics study. *Proteins-Structure Function and Bioinformatics*, 79(5), 1649-1661.

- Bellesia, Giovanni and Jewett, Andrew I. and Shea, Joan-Emma. (2011). Relative stability of de novo four-helix bundle proteins: Insights from coarse grained molecular simulations. *Protein Science*, 20(5), 818-826.

- Chan, Henry and Kral, Petr. (2011). Self-standing nanoparticle membranes and capsules. *Nanoscale*, 3(4), 1881-1886.

- Prasad, Nirmal K. and Vindal, Vaibhav and Kumar, Vikash and Kabra, Ashish and Phogat, Navneet and Kumar, Manoj. (2011). Structural and docking studies of Leucaena leucocephala Cinnamoyl CoA reductase. *Journal of Molecular Modeling*, 17(3), 533-541.

- Firlej, Lucyna and Kuchta, Bogdan and Roth, Michael W. and Wexler, Carlos. (2011). Molecular simulations of intermediate and long alkanes adsorbed on graphite: Tuning of non-bond interactions. *Journal of Molecular Modeling*, 17(4), 811-816.

- Qu, Zheng-Wang and Zhu, Hui and May, Volkhard. (2011). Vibrational Spectral Signatures of Peptide Secondary Structures: N-methylation and Side chain Hydrogen Bond in Cyclosporin A. *Journal of Computational Chemistry*, 32(8), 1500-1518.

- Walch, Stephen P. (2011). Effect of Solvation on the Oxygen Reduction Reaction on Pt Catalyst. *Journal of Physical Chemistry C*, 115(15), 7377-7391.

- Staritzbichler, Rene and Anselmi, Claudio and Forrest, Lucy R. and Faraldo-Gomez, Jose D. (2011). GRIFFIN: A Versatile Methodology for Optimization of Protein-Lipid Interfaces for Membrane Protein Simulations. *Journal of Chemical Theory and Computation*, 7(4), 1167-1176.

- Prates, Erica T. and Souza, Paulo C. T. and Pickholz, Monica and Skaf, Munir S. (2011). CHARMM-Based Parameterization of Neutral Articaine-A Widely Used Local Anesthetic. *International Journal Of Quantum Chemistry*, 111(7-8, Sp. Iss. SI), 1339-1345.

- Hansson, Anders and Souza, Paulo C. T. and Silveira, Rodrigo L. and Martinez, Leandro and Skaf, Munir S. (2011). CHARMM Force Field Parameterization of Rosiglitazone. *International Journal Of Quantum Chemistry*, 111(7-8, Sp. Iss. SI), 1346-1354.

- Fezoua-Boubegtiten, Zahia and Desbat, Bernard and Brisson, Alain and Gounou, Celine and Laguerre, Michel and Lecomte, Sophie. (2011). Effect of Mg2+ versus Ca2+ on the behavior of Annexin A5 in a membrane-bound state. *European Biophysics Journal with Biophysics Letters*, 40(5), 641-649.

- Moss, Christopher L. and Chung, Thomas W. and Cerovsky, Vaclav and Turecek, Frantisek. Electron Transfer Dissociation of a Melectin Peptide: Correlating the Precursor Ion Structure with Peptide Backbone Dissociations. (2011). *Collection of Czechoslovak Chemical Communications*, 76(4), 295-309.

- Jang, Hyunbum and Arce, Fernando Teran and Mustata, Mirela and Ramachandran, Srinivasan and Capone, Ricardo and Nussinov, Ruth and Lal, Ratnesh. (2011). Antimicrobial Protegrin-1 Forms Amyloid-Like Fibrils with Rapid Kinetics Suggesting a Functional Link. *Biophysical Journal*, 100(7), 1775-1783.

- Lee, Jun Hyuck and Park, HaJeung and Park, Soo Jeong and Kim, Hak Jun and Eom, Soo Hyun. (2011). The structural flexibility of the shank1 PDZ domain is important for its binding to different ligands. *Biochemical and Biophysical Research Communications*, 407(1), 207-212.

- Silvestre-Ryan, Jordi and Lin, Yuchun and Chu, Jhih-Wei. (2011). "Fluctuograms" Reveal the Intermittent Intra-Protein Communication in Subtilisin Carlsberg and Correlate Mechanical Coupling with Co-Evolution. *PLOS Computational Biology*, 7(3).

- Nurminen, Elisa M. and Pihlavisto, Marjo and Lazar, Laszlo and Pentikainen, Ulla and Fueloep, Ferenc and Pentikainen, Olli T. (2011). Novel Hydrazine Molecules as Tools To Understand the Flexibility of Vascular Adhesion Protein-1 Ligand-Binding Site: Toward More Selective Inhibitors. *Journal of Medicinal Chemistry*, 54(7), 2143-2154.

- Zhao, Xiongce. (2011). Self-Assembly of DNA Segments on Graphene and Carbon Nanotube Arrays in Aqueous Solution: A Molecular Simulation Study. *Journal of*

Physical Chemistry C, 115(14), 6181-6189.

- Wedberg, Rasmus and O'Connell, John P. and Peters, Gunther H. and Abildskov, Jens. (2011). Total and direct correlation function integrals from molecular simulation of binary systems. *Fluid Phase Equilibria*, 302(1-2, Sp. Iss. SI), 32-42.

- Vattulainen, Ilpo and Rog, Tomasz. (2011). Lipid Simulations: A Perspective on Lipids in Action. *Cold Spring Harbor Perspectives in Biology*, 3(4).

- Geppert, Tim and Hoy, Benjamin and Wessler, Silja and Schneider, Gisbert. (2011). Context-Based Identification of Protein-Protein Interfaces and "Hot-Spot" Residues. *Chemistry & Biology*, 18(3), 344-353.

- Song, Sang-Hun and Freddolino, Peter L. and Nash, Abigail I. and Carroll, Elizabeth C. and Schulten, Klaus and Gardner, Kevin H. and Larsen, Delmar S. (2011). Modulating LOV Domain Photodynamics with a Residue Alteration outside the Chromophore Binding Site. *Biochemistry*, 50(13), 2411-2423.

- Mazars, Martial. (2011). Long ranged interactions in computer simulations and for quasi-2D systems. *Physics Reports-Review Section of Physics Letters*, 500(2-3), 43-116.

- Gonzalez, Angel and Murcia, Marta and Benhamu, Bellinda and Campillo, Mercedes and Lopez-Rodriguez, Maria L. and Pardo, Leonardo. (2011). The importance of solvation in the design of ligands targeting membrane proteins. *Medchemcomm*, 2(3), 160-164.

- Moss, Christopher L. and Chung, Thomas W. and Wyer, Jean A. and Nielsen, Steen Brondsted and Hvelplund, Preben and Turecek, Frantisek. (2011). Dipole-Guided Electron Capture Causes Abnormal Dissociations of Phosphorylated Pentapeptides. *Journal of the American Society for Mass Spectrometry*, 22(4), 731-751.

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 2010 - March 2011) the web site home pages for the Resources VMD[†], NAMD[‡], and BioCoRE[§] softwares showed substantial visitor traffic, as depicted

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

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

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

in Table 1.

	Total	Month Avg.
VMD	241,578	20,131
NAMD	127,022	10,585
BioCoRE	17,246	1,437

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 2010 to April 2011, the Resource has hosted 9 visitors[¶]. Visitors fund their visits, while the Resource contributes computing resources, facilities, and local expertise.

- *User Support*
  The Resource strives to release code of high quality, and to distribute bug-free software to the user community. Assisting use in assuring the integrity and reliability of our software is a local prototyping phase, in which Resource members make use of early releases of code and provide feedback to developers before broader release occurs. In terms of providing support to the continually expanding external user community (over 234,000 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 2010-2011

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

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

Between May 2010 and April 2011 the Resource organized and hosted 25 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 29, 2011, Vita Solovyeva, Germany, *Disorder and phase transition phenomena in thin films of organic charge transfer compounds*
- Apr 25, 2011, Professor Massimo Olivucci, Bowling Green State University, Bowling Green, OH, *From Computational Photobiology to the Development of Biomimetic Molecular Devices*
- Apr 11, 2011, Professor Thomas Woolf, John Hopkins University , Baltimore, MD, *Dynamic Importance Sampling for Biomolecular Transitions*
- Apr 4, 2011, Professor So Hirata, University of Illinois Urbana-Champaign, Urbana, IL, *Why is energy extensive? A quantum chemist's view*
- Apr 1, 2011, Professor Hans-Joachim Werner, University of Stuttgart, Stuttgart, Germany, *Explicitly Correlated Wave Function Methods for Large Molecules*
- Mar 28, 2011, Dr. Christophe Chipot, Nancy University, Vandoeuvre-les-Nancy, France, *Recent advances in the understanding of mitochondrial transport*
- Mar 14, 2011, Professor Irina I. Serysheva, The University of Texas Medical School at Houston, Houston, TX, *Flexible Architecture of Ca2+ Release Channels by Cryo-EM*
- Feb 28, 2011, Professor Ken A. Dill, Stony Brook University, New York, NY, *Dynamical laws applied to few-particle systems in bio- and nano-science*
- Feb 21, 2011, Professor Chris Adami, Keck Graduate Institute, Claremont, CA, *A Brief History of Digital Life*
- Feb 14, 2011, Professor Allen Buskirk, Brigham Young University, Provo, Utah, *Nascent peptide sequences that stall ribosomes during protein synthesis*
- Jan 24, 2011, Professor Wompil Im, The University of Kansas, Lawrence KS, *Mechanisms and Energetics of Protein/Peptide Interactions in Biological Membranes*

- Dec 13, 2010, Dr. Julio Ortiz, Max Plank Institute of Biochemistry, Germany, *From isolated molecules to intact cells - Structure of ribosomal arrangements in vitro and in situ*
- Dec 6, 2010, Dr. Wouter Hoff, Oklahoma State University, Stillwater, OK, *High-throughput biophysics for understanding functional tuning in proteins*
- Nov 15, 2010, Dr. Ron Elber, Institute of Computational Sciences and Engineering (ICES), University of Texas at Austin, TX, *Milestoning: A theory and algorithm for atomically detailed long time dynamics of biological molecules*
- Nov 1, 2010, Professor George Biros, Georgia Institute of Technology and Emory University, Atlanta, GA, *Fast algorithms for three-dimensional vesicle flow simulations*
- Oct 18, 2010, Professor Michael Feig, Michigan State University, East Lansing, MI, *Dynamics of membrane-bound peptides from computer simulations*
- Oct 18, 2010, Professor Terry Hwa, University of California at San Diego, San Diego, CA, *Bacterial growth control: theory and experiments*
- Oct 18, 2010, Professor Thomas T. Perkins, , Boulder, CO, *Advances and limitations in force spectroscopy of bio-molecules*
- Oct 11, 2010, Professor Peter Ortoleva, Indiana University, Bloomington, IN, *Understanding Nanosystems the Multiscale Way: Applications to Macromolecular Assemblies and Quantum Nanoparticles*
- Sep 27, 2010, Associate Prof. Ioan Kosztin, University of Missouri - Columbia , Columbia, MO, *Multiscale modeling of the dynamics of multicellular systems*
- Sep 17, 2010, Professor Iwao Ohmine, Institute for Molecular Science, Myodaiji, Okazaki, Japan, *Water water everywhere; water dynamics in phase transitions, and chemical and biomolecular reactions*
- Aug 23, 2010, Dr. Tohru Kozasa, University of Illinois, Chicago, Chicago, IL, *Molecular mechanism of activation of PLC-beta by Gq*
- Aug 23, 2010, Professor Bob Eisenberg, Rush University, Chicago, IL, *Self-organized selectivity in Calcium and Sodium Channels*
- Aug 18, 2010, Dr. Keren Lasker, University of California at San Francisco , San Francisco, CA, *Determining macromolecular assembly structures by molecular docking and fitting into an electron density map*

- May 3, 2010, Dr. Tohru Kozasa, University of Illinois at Chicago, Chicago, IL, *Dynamics of GPCR Signaling System: A key to Maintain our Life*

Awards, Honors, and Special Recognitions

There are no items to list for the current year.

Dissemination

- 66 published articles and 12 in press in refereed journals or other publications
- Over 705,926 unique visitors to the Resource web site
- Over 22,889 article downloads from the Resource's publications database
- 577 reprint requests fulfilled by Resource staff
- 62 talks by Resource faculty and 14 presentations by other members
- 28 news stories about the Resource in various media outlets
- 45 requests to use Resource images or movies from external publishers or presenters
- Over 29,534 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 12 articles currently in press and 66 published articles by Resource members and collaborators published over the last funding period.

Articles In Press

- Xabier Agirrezabala, Eduard Scheiner, Leonardo G. Trabuco, Jianlin Lei, Rodrigo F. Ortiz-Meoz, Klaus Schulten, Rachel Green, and Joachim Frank. Structural insights into cognate vs. near-cognate discrimination during decoding. *EMBO Journal*, 2011. In press.
- J. Boettcher, R. Davis-Harrison, M. Clay, A. Nieuwkoop, Y. Z. Ohkubo, E. Tajkhorshid, J. H. Morrissey, and Chad Rienstra. Atomic View of Calcium-Induced Clustering of Phosphatidylserine in Mixed Lipid Bilayers. *Biochemistry*, 2011. In press.
- Jens Frauenfeld, James Gumbart, Eli O. van der Sluis, Soledad Funes, Marco Gartmann, Birgitta Beatrix, Thorsten Mielke, Otto Berninghausen, Thomas Becker, Klaus Schulten, and Roland Beckmann. Cryo-EM structure of the ribosome-SecYE complex in the membrane environment. *Nature Structural & Molecular Biology*, 2011. In press.
- James Gumbart, Christophe Chipot, and Klaus Schulten. Free energy of nascent-chain folding in the translocon. *Journal of the American Chemical Society*, 2011. In press.

- James Gumbart, Eduard Schreiner, Leonardo G. Trabuco, Kwok-Yan Chan, and Klaus Schulten. Viewing the mechanisms of translation through the computational microscope. In Joachim Frank, editor, Molecular Machine in Biology. Cambridge University Press, 2011. In press.

- Shigehiko Hayashi and Klaus Schulten. Quantum biology of retinal proteins. In Masoud Mohseni, Yasser Omar, Greg Engel, and Martin B. Plenio, editors, Quantum Effects in Biology. Cambridge University Press, 2011. To be published.

- Z. Huang, S. A. Shaikh, P.-C. Wen, G. Enkavi, J. Li, and E. Tajkhorshid. Membrane Transporters - Molecular Machines Coupling Cellular Energy to Vectorial Transport Across the Membrane. In Benoit Roux, Editor, Molecular Machines. World Scientific, 2011. In press.

- Ulrich Kleinekathoefer, Barry Isralewitz, Markus Dittrich, and Klaus Schulten. Domain motion during the equilibration of individual F_1-ATPase b-subunits. *Journal of Physical Chemistry*, 2011. In press.

- Ilia A. Solov'yov, P. J. Hore, Thorsten Ritz, and Klaus Schulten. A chemical compass for bird navigation. In Masoud Mohseni, Yasser Omar, Greg Engel, and Martin B. Plenio, editors, Quantum Effects in Biology, chapter 10. Cambridge University Press, 2011. To be published.

- Johan Strumpfer, Jen Hsin, Melih Sener, Danielle Chandler, and Klaus Schulten. Introduction to a quantum biological device, the light harvesting apparatus in purple photosynthetic bacteria. In Benoit Roux, editor, Molecular Machines. World Scientific Press, 2011. In press.

- David E. Tanner, Wen Ma, Zhongzhou Chen, and Klaus Schulten. Theoretical and computational investigation of flagellin translocation and bacterial flagellum growth. *Biophysical Journal*, 2011. In press.

- Gregory Timp, Utkur Mirsaidov, Winston Timp, Jiwook Shim, Deqiang Wang, Valentin Dimitrov, Jan Scrimgeour, Chunchen Lin, Jeffrey Comer, Anthony Ho, Xueqing Zou, Aleksei Aksimentiev, and Klaus Schulten. 3rd generation DNA sequencing with a nanopore. In Samir M. Iqbal and Rashid Bashir, editors, Nanopores: Sensing and Fundamental Biological Interactions. Springer, Berlin, 2011. In press.

Published Articles

- Aksimentiev, Alek. Deciphering ionic current signatures of DNA transport through a nanopore. *Nanoscale* 2:468483, 2010. (PMC: 2909628)

- Rebecca W. Alexander, John Eargle, and Zaida Luthey-Schulten. Experimental and computational analysis of tRNA dynamics, *FEBS Letters*, 584:376-386, 2010.

- Rogan Carr, Jeffrey Comer, Mark D. Ginsberg and Alek Aksimentiev. Modeling pressure-driven transport of proteins through a nanochannel. *IEEE Transactions on Nanotechnology*, 10:75-82, 2011.

- Ke Chen, John Eargle, Krishnarjun Sarkar, Martin Gruebele, and Zaida Luthey-Schulten. Functional role of ribosomal signatures. *Biophysical Journal*, 99:3930-3940, 2010.

- Wei Chen, Jizhong Lou, Jen Hsin, Klaus Schulten, Stephen C. Harvey, and Cheng Zhu. Molecular dynamics simulations of forced unbending of integrin $a_V b_3$. *PLoS Comput. Biol.*, 7:e1001086, 2011. (PMC: 3040657)

- Eduardo R. Cruz-Chu and Klaus Schulten. Computational microscopy of the role of protonable surface residues in nanoprecipitation oscillations. *ACS Nano*, 4:4463-4474, 2010. (PMC: 2927718)

- Jiankuai Diao, Andrew J. Maniotis, Robert Folberg, and Emad Tajkhorshid. Interplay of mechanical and binding properties of fibronectin type I. *Theoretical Chemistry Accounts*, 125:397-405, 2010. (NIHMS: 222485)

- Giray Enkavi and Emad Tajkhorshid. Simulation of spontaneous substrate binding revealing the binding pathway and mechanism and initial conformational response of GlpT. *Biochemistry*, 49:1105-1114, 2010. (PMC: 2829668).

- Jeremy Enos, Craig Steffen, Joshi Fullop, Michael Showerman, Guochun Shi, Kenneth Esler, Volodymyr Kindratenko, John E. Stone, and James C. Phillips. Quantifying the Impact of GPUs on Performance and Energy Efficiency in HPC Clusters. GREENCOMP '10 Proceedings of the International Conference on Green Computing, IEEE Computer Society Washington, DC, USA, pp. 317-324, 2010.

- Peter L. Freddolino, Christopher B. Harrison, Yanxin Liu, and Klaus Schulten. Challenges in protein folding simulations: Force field, timescale, sampling, and analysis. *Nature Physics*, 6:751-758, 2010. (NIHMS: 263745)

- Jianhua Feng, Eliana Lucchinetti, Giray Enkavi, Yi Wang, Peter Gehrig, Bernd Roschitzki, Marcus C. Schaub, Emad Tajkhorshid, Kathrin Zaugg, and Michael Zaugg. Tyrosine phosphorylation by Src within the cavity of the adenine nucleotide translocase 1 regulates ADP/ATP exchange in mitochondria. *American Journal of Physiology - Cell Physiology*, 298:740-748, 2010.

- Isaac Gelado, John E. Stone, Javier Cabezas, Sanjay Patel, Nacho Navarro, and Wen-mei W. Hwu. An Asymmetric Distributed Shared Memory Model for Heterogeneous Parallel Systems. ASPLOS '10: Proceedings of the 15th International Conference on Architectural Support for Programming Languages and Operating Systems, ACM New York, NY, USA, pp. 347-358, 2010.

- James Gumbart, Christophe Chipot, and Klaus Schulten. Free-energy cost for translocon-assisted insertion of membrane proteins. *Proceedings of the National Academy of Sciences, USA*, 108:3596-3601, 2011. (PMC3048118)

- David J. Hardy, John E. Stone, Kirby L. Vandivort, David Gohara, Christopher Rodrigues, and Klaus Schulten. Fast molecular electrostatics algorithms on GPUs. In Wen-Mei Hwu, editor, GPU Computing Gems, chapter 4, pp. 43-58. Morgan Kaufmann Publishers, 2011.

- Jen Hsin and Klaus Schulten. Improved resolution of tertiary structure elasticity in muscle protein. *Biophysical Journal*, 100:L22-L24, 2011. (PMC3037604)

- Jen Hsin, Johan Strumpfer, Eric H. Lee, and Klaus Schulten. Molecular origin of the hierarchical elasticity of titin: simulation, experiment and theory. *Annual Review of Biophysics*, 40:187-203, 2011.

- Jen Hsin, Johan Strumpfer, Melih Sener, Pu Qian, C. Neil Hunter, and Klaus Schulten. Energy transfer dynamics in an RC-LH1-PufX tubular photosynthetic membrane. *New Journal of Physics*, 12:085005, 2010. (19 pages). (PMC: 2997751)

- Zhijian Huang and Emad Tajkhorshid (2010) Identification of the Third Na^+ Site and the Sequence of Extracellular Binding Events in the Glutamate Transporter. *Biophysical Journal*, 99: 1416-1425, 2010.

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- Carsten Olbrich, Johan Strumpfer, Klaus Schulten, and Ulrich Kleinekathoefer. Quest for spatially correlated fluctuations in the FMO light-harvesting complex. *Journal of Physical Chemistry B*, 115:758-764, 2011. (NIHMS: 258259)

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- Hans-C. Siebert, Monika Burg-Roderfeld, Thomas Eckert, Sabine Stötzel, Ulrike Kirch, Tammo Diercks, Martin J. Humphries, Martin Frank, Rainer Wechselberger, Emad Tajkhorshid, and Steffen Oesser. Interaction of the α2A domain of integrin with small collagen fragments. *Protein and Cell*, 1:393-405, 2010.

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- John E. Stone, Axel Kohlmeyer, Kirby L. Vandivort, and Klaus Schulten. Immersive molecular visualization and interactive modeling with commodity hardware. *Lecture Notes in Computer Science*, 6454:382-393, 2010. (PMC: 3032211)

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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 705,926 unique visitors to the Resource web site, an average of 74,359 per month during the April 2010 – March 2011 period; visits during that period resulted in 3.38 terabytes of data transfer (from downloaded pages, images, and files within the site, and excluding robots, worms, or replies with special HTTP status codes). The most visited sections of the web site are shown in Table 2.

A recent Yahoo! site search (April, 2011) found that 16,976 external sites link into areas of the Resource web site, with 1,409 sites linking directly to the home page.

	Total Visitors	Visitors per Month
VMD	241,578	20,131
NAMD	127,022	10,585
BioCoRE	17,246	1,437
Other Research	167,706	13,975
Galleries	24,699	2,058
Publications	40,003	3,333
Seminars	5,856	488

Table 2: Web site visitors from April 2010 - March 2011

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 22,889 unique visitors downloaded at least one file copy of an article using the database over the April 2010 – March 2011 period. Additionally, 577 reprint requests were handled directly by Resource staff, primarily by posting electronic files in a manner that respects copyright restrictions. The Resource also receives numerous requests each year by scientists who want to use materials from the Resource website image or movie gallery for their work; 45 such requests were received over the April 2010 – March 2011 period.

Lectures, Presentations and Posters

The Resource PIs and other members gave the following lectures, presentations, or posters over the April 2010 - March 2011 period†:

Klaus Schulten

- June 2011, Albany, New York, Albany 2011: Conversation 17
  Lecture: "Computational Microscopy"
- May 2011, Munich, Germany, Leopoldina Meeting Quantum Technologies
  Lecture: "What Quantum Technology Can Learn from Quantum Biology of Light Harvesting Light Reception, and Magnetic Field Reception"
- April 2011, Simon Fraser University, Vancouver, British Columbia
  Lecture: "The Computational Microscope Images Biomolecular Machines and Nanodevices"

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

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

- April 2011, University of British Columbia, Vancouver, British Columbia, Pacific Institute for Theoretical Physics
  Lecture: "A Quantum Biological Device - The Light Harvesting Apparatus of Purple Photosynthetic Bacteria"

- April 2011, University of British Columbia Vancouver, Canada, Pacific Institute for Theoretical Physics
  Lecture: "Quantum Computing and Animal Navigation"

- March 2011, Atlanta, GA, Georgia Institute of Technology, Hands-on Workshop on Computational Biophysics at Atlanta
  Lecture: "Introduction to Protein Structure and Dynamics"
  Lecture: "Statistical Mechanics of Proteins"

- March 2011, New York, NY, New York Academy of Sciences
  Lecture: "Viewing the Ribosome Through the Computational Microscope"

- March 2011, Baltimore, MD, Biophysical Society 55th Annual Meeting
  Lecture: "Sculpting Cellular Membranes From Inside or Outside"

- November-December 2010, Urbana, IL, University of Illinois, Beckman Institute, 'Hands-on Workshop on Computational Biophysics at Urbana
  Lecture: "Structure and Sequence Analysis with VMD"
  Lecture: "Analysis of Equilibrium and Non-equilibrium Properties of Proteins with NAMD"

- November 2010, Urbana, IL, University of Illinois, Beckman Institute, 'Hands-on Workshop on Computational Biophysics at Urbana
  Lecture: "Structure and Sequence Analysis with VMD"
  Lecture: "Analysis of Equilibrium and Non-equilibrium Properties of Proteins with NAMD"

- October 2010, New York, NY, Department of Structural and Chemical Biology, Mount Sinai School of Medicine
  Lecture: "Discoveries Through the Computational Microscope"

- September 2010, Cape Cod, MA, Joachim Frank 70th Birthday Celebration
  Lecture: "Molecular Dynamics Studies of the Ribosome"

- September 2010, San Jose, CA NVIDIA GPU Technology Conference 2010 - Research Track of GTC
  Lecture: "The Computational Microscope"

- September 2010, Detroit Michigan, Wayne State University School of Medicine
  Lecture: "The Computational Microscope Images Biomolecular Machines and Nanodevices"

- August 2010, Irvine, CA S.H. White Symposium - Frontiers in Membrane and Membrane Protein Biophysics: Experiments and Theory
  Lecture: "Molecular Dynamics and Electron Microscopy Studies of Nascent Membrane Proteins in the Ribosome SecY complex"

- August 2010, Evanston, IL, Northwestern University, Chemistry Department, Network for Computational Nanotechnology Distinguished Lecture Series
  Lecture: "Computer Modeling in Biotechnology, a Partner in Development"

- July 2010, San Diego, CA, The Scripps Research Institute, National Resource for Automated Molecular Microscopy 'Hands-on' Workshop on Computational Biophysics
  Lecture: "Introduction to Protein Structure and Dynamics"
  Lecture: "Statistical Mechanics of Proteins"

- July 2010, Edmonton, AB, Canada, Canadian Symposium on Theoretical Chemistry
  Lecture: "Quantum Biology of Photosynthesis in Purple Bacteria"

- July 2010, Bremen, Germany, Jacobs University Bremen, Workshop / Transport across Membranes
  Lecture: "Molecular Dynamics Studies of unusual Membrane Transport"

- June 2010, Barga, Italy, Gordon Research Conference
  Lecture: "Single Molecule Approaches to Biology"

- June 2010, Munich, Germany, Ludwig-Maximilian Universität
  Lecture: "The Computational Microscope"

- May 2010, Pittsburgh, PA, National Resource for Biomedical Supercomputing, 'Hands-on' Workshop on Computational Biophysics
  Lecture: "Introduction to Protein Structure and Dynamics"
  Lecture: "Statistical Mechanics of Proteins"

- May 2010, Urbana, IL, CNST Annual Nanotechnology Workshop
  Lecture: "Molecular Control of Ionic Conduction in Polymer Nanopores"

- May 2010, Cambridge, MA, Harvard University Reunion of Roy Gordon's Group
  Lecture: "From Three to Three Million Atoms"

Laxmikant Kale

- December, 2010, Goa, India, HiPC 2010
  Lecture: "A Study of Memory-Aware Scheduling in Message Driven Parallel Programs"
  Lecture: "Automated Mapping of Regular Communication Graphs on Mesh Interconnects"

Zan Luthey-Schulten

- April 2011, Karlsruhe, Germany, VAAM (Verein.Allgem.Angewandt.Mikrobio)
  Lecture: "Towards in Silico Cells: Simulating Processes in Entire Bacterial Cells"
- March 2011, Atlanta, GA, Georgia Institute of Technology, 'Hands-on Workshop on Computational Biophysics at Atlanta
  Lecture: "Introduction to Bioinformatics"
- March 2011, New York, NY, New York Academy of Sciences
  Lecture: "Towards in Silico Cells: Simulating Processes in Entire Bacterial Cells"
- January, 2011, Venture, CA, Gordon Research Conference: Stochastic Physics in Biology
  Lecture: "Modeling Biochemical Processes in Bacterial Cells"
- January 24, 2011, Los Alamos, NM, Los Alamos National Laboratory, T6 Biophysics Division
  Lecture: "Dynamical Networks in Translation: From Molecules to Cells"
- November-December 2010, Urbana, IL, University of Illinois, Beckman Institute, 'Hands-on Workshop on Computational Biophysics at Urbana
  Lecture: "Introduction to Bioinformatics"
- November 2010, Urbana, IL, University of Illinois, Beckman Institute, 'Hands-on Workshop on Computational Biophysics at Urbana
  Lecture: "Introduction to Bioinformatics"
- September 2010, Venice, Italy, VIU, CeNS Workshop on Nanosciences: Merging Disciplines
  Lecture: "Dynamical Networks in Translation: From Molecules to Cells"
- July 2010, Knoxville, TN, University of Tennessee, Summer School in Biophysics
  Lecture: "Simulations and Visualization of Dynamics in RNA:Protein Complexes"

- June 2010, Munich, Germany, Applied Physics Institute of Professor Hermann Gaub, LMU
  Lecture: "Multiscale Simulations of Translation and Other Cellular Processes"

- May 2010, Bochum, Germany, Leopoldina Symposium - The Complexity Connecting Biomolecular Structure and Solvation Dynamics
  Lecture: "Role of Solvation on tRNA Dynamics and Migration"

Emad Tajkhorshid

- April 2011, Washington, DC, Invited talk at Gas Channels symposium, Experimental Biology 2011
  Lecture: "Molecular Dynamics Simulations of Gas Transport Through Membrane Channels"

- April 2011, Erlangen, Germany, Plenary lecture at 25th Molecular Modelling Workshop
  Lecture: "Dynamical View of Energy Coupling Mechanisms in Active Membrane Transporters"

- March 2011, Anaheim, CA, Invited talk at 241st National Meeting of the American Chemical Society
  Lecture: "Molecular Mechanisms of Energy Coupling in Active Membrane Transporters"

- February 2011, Urbana, IL, University of Illinois at Urbana-Champaign, Department of Molecular and Integrative Physiology
  Lecture: "Dynamical View of Energy Coupling Mechanisms in Active Membrane Transporters"

- November-December 2010, Urbana, IL, University of Illinois, Beckman Institute, 'Hands-on Workshop on Computational Biophysics at Urbana
  Lecture: "Parameters for Classical Force Fields"
  Lecture: "Simulating Membrane Channels"

- November 2010, Urbana, IL, University of Illinois, Beckman Institute, 'Hands-on Workshop on Computational Biophysics at Urbana
  Lecture: "Parameters for Classical Force Fields"
  Lecture: "Simulating Membrane Channels"

- October 2010, Urbana, IL, Beckman Institute, Invited lecture at "Imaging Without Boundaries
  Lecture: "Visualizing the Art of Active Transport Across the Cellular Membrane"

- September 2010, Oxford, England, Invited lecture at International Conference on "Celebrating Computational Biology: A Tribute to Frank Blaney
  Lecture: "Combining Different Time and Resolution Scales to Describe Functionally Relevant Structural Transitions in Membrane Proteins"

- August 2010, Biddeford, ME, University of New England at Biddeford, Invited lecture at Gordon Research Conference on Membrane Transport Proteins
  Lecture: "A Dynamical View of Membrane Transporter Function"

- July 2010, San Diego, CA, The Scripps Research Institute, National Resource for Automated Molecular Microscopy 'Hands-on' Workshop on Computational Biophysics
  Lecture: "Parameters for Classical Force Fields"
  Lecture: "Simulating Membrane Channels"

- July 2010, Knoxville, TN, Invited lecture at "Summer School in Biophysics at UT/ORNL: Computational and Experimental Challenges
  Lecture: "Visualizing the Art of Active Transport Across Cellular Membranes at Sub-Angstrom Resolution"

- June 2010, Traverse City, MI, Invited lecture at "From Computational Biophysics to Systems Biology - CBSB10"
  Lecture: "Dynamical View of Energy Coupling Mechanisms in Active Membrane Transporters"

- May 2010, Chicago, IL, BIO International Convention 2010, McCormick Place
  Lecture: "Next Generation Drug Design by Large-Scale Simulation of Biomolecules"

- May 2010, Pittsburgh, PA, National Resource for Biomedical Supercomputing, 'Hands-on' Workshop on Computational Biophysics
  Lecture: "Parameters for Classical Force Fields"
  Lecture: "Simulating Membrane Channels"

Aleksei Aksimentiev

- September 2010, Urbana, IL, Beckman Institute for Advanced Science and Technology, Director's Seminar
  Lecture: "Sequencing a DNA Molecule Using a Nanopore"

- August 2010, France, Ile de Berder, Summer School "Biosensing with Channels"
  Lecture: "Modeling Transport of Biomolecules Through Nanopores and Nanochannels"

- April 2010, Netherlands, Delft University of Technology, Department of Bionanoscience
  Lecture: "Deciphering Ionic Current Signatures of DNA Transport Through a Nanopore"

Other TCB members (includes meetings attended and poster sessions)

- September 2010, Urbana, IL, University of Illinois, Beckman Institute, Nanohour Seminar
  Lecture: "Computational Microscopy of Synthetic Nanopores" (Eduardo Cruz-Chu)

- September 17, 2010, Oak Ridge, TN, Oak Ridge National Laboratory, Bio-molecular Simulations on Future Computing Architectures
  Lecture: "Simulating Biomolecules on GPUs with the Multilevel Summation Method" (David Hardy)

- August 2010, Urbana, IL, University of Illinois, Center for Physics of Living Cells, CPLC Post-Doc and Graduate Student Symposium
  Lecture: "Interplay of L1Stalk and tRNA on the Ribosome" (Bo Liu)

- August 2010, Urbana, IL, Beckman Institute, Workshop on GPU Programming for Molecular Modeling
  Lecture: "Introductory Lecture, Participant Introductions" (John Stone)
  Lecture: "GPU Particle-Grid Algorithms: Electrostatics" (John Stone)
  Lecture: "GPU Particle-Particle Algorithms: Non-bonded Force Calculation" (David Hardy)
  Lecture: "GPU Histogramming: Radial Distribution Functions" (John Stone)
  Lecture: "CUDA Algorithms for Stochastic Simulation of Biochemical Reactions" (Andrew Magis)
  Lecture: "Single-Node Multi-GPU Algorithms: Molecular Orbitals" (John Stone)
  Lecture: "NAMD: Molecular Dynamics on GPU Clusters" (Jim Phillips)

- July 2010, Urbana, IL, University of Illinois at Urbana-Champaign, Universal Parallel Computing Research Center, 2010 Universal Parallel Computing Research Center Summer School
  Lecture: "The OpenCL Programming Model, Part 1" (John Stone)
  Lecture: "The OpenCL Programming Model, Part 2" (John Stone)

- July 2010, Edinburgh, Scotland, University of Edinburgh, Multiscale Molecular Modeling
  Lecture: "Using GPUs to Compute the Multilevel Summation of Electrostatic Forces" (David Hardy)

- June 2010, Traverse City, MI, "From Computational Biophysics to Systems Biology - CBSB10"
  Lecture: "The Dimeric Photosynthetic Core Complex Generates Tubular Curvature in Bacterial Membranes" (Jen Hsin)

Media Coverage

Stories involving the Resource appeared in popular media, online news sources, and other outlets during April 2010 – March 2011. The Resource received press interest for research by faculty member Aleksei Aksimentiev in developing cheaper, faster method for DNA sequencing, with the project receiving 10 million processor hours on the Oak Ridge National Laboratory's Jaguar supercomputer via an INCITE grant[‡]. Resource Director Klaus Schulten also received press for his keynote lecture at the 2010 NVIDIA GPU Technology Conference[§], and the Resource's work on cryptochrome and avian navigation was covered by the *Wired* news site[¶].

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

- Kerns, C. (February 24, 2011). Whole-genome sequencing simulated on supercomputers. Scientists work to make personalized genomics affordable and quick for patients.*Oak Ridge National Laboratory News Release.*
  `http://www.ornl.gov/info/features/get_feature.cfm?FeatureNumber=f20110224-00`
  - Staff. (February 25, 2011). Whole-Genome sequencing simulated on supercomputers. *PhysOrg.com.*
    `http://www.physorg.com/news/2011-02-whole-genome-sequencing-simulated-supercomputers.html`
  - Staff. (February 25, 2011). Scientists work to make personalized genomics affordable for patients.*R&D Magazine.*
    `http://www.rdmag.com/News/2011/02/Information-Technology-Genomics-Scientists-Work-To-Make-Personalized-Genomics-Affordable-For-Patients/`

[‡] `http://www.ornl.gov/info/features/get_feature.cfm?FeatureNumber=f20110224-00`

[§] `http://www.hpcwire.com/hpcwire/2010-09-23/gpu\_tech\_conference\_wrap-up.html`

[¶] `http://www.wired.com/wiredscience/2011/01/quantum-birds/`

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

- Humber, A. (February 10, 2011). GPU-Powered Science and Innovation Drive GPU Technology Conference 2011. Conference to Feature High-Performance Computing Symposium Co-Hosted by Los Alamos National Lab and NVIDIA. *Marketwire.* `http://www.marketwire.com/press-release/GPU-Powered-Science-and-Innovation-Drive-GPU-Technology-Conference-2011-NASDAQ-NVDA-1393692.htm`

- Brueckner, R. (February 2, 2011). Coders tool up for 10 petaflop Blue Waters supercomputer. *The Register.* `http://www.theregister.co.uk/2011/02/02/ncsa_blue_waters_supercomputer/`

- Bates, D. (January 28, 2011). Birds use quantum theory to literally 'see' Earth's magnetic field as they fly.*MailOnline.* `http://www.dailymail.co.uk/sciencetech/article-1351429/Birds-use-quantum-theory-literally-Earths-magnetic-field-fly.html?ito=feeds-newsxml`

- Grossman, L. (January 27, 2011). In the blink of birds eye, a model for quantum navigation. *Wired Science.* `http://www.wired.com/wiredscience/2011/01/quantum-birds/`

- Talkington, L. (December 13, 2010). Illinois researcher named 2010 CUDA Fellow by NVIDIA.*UIUC Coordinated Science Laboratory Press Release.* `http://www.csl.uiuc.edu/news/illinois-researcher-named-2010-cuda-fellow-nvidia`

- Shen, N. (December 7, 2010). TCB workshops continue to evolve as successful educational program. *Beckman Institute News and Events.* `http://www.beckman.illinois.edu/news/TCBworkshopstory`

- May, M. (November 16, 2010). Speeding up Science. Many of todays most difficult scientific computations include some gain from GPUs. *Scientific Computing.* `http://www.scientificcomputing.com/articles-HPC-Speeding-up-Science-111510.aspx\`

- Wolf, L. (November 1, 2010). The GPU Revolution. Designed for video games, Graphics Processing Units bring once-impossible simulations within reach for chemists.*C&EN.* `http://pubs.acs.org/cen/science/88/8844sci1.html`

- Robertson, B. (October 11, 2010). Inside Track. *Computer Graphics World.* `http://www.cgw.com/Publications/CGW/2010/Volume-33-Issue-9-October-`

2010-/Inside-Track.aspx

- Feldman, M. (September 23, 2010). GPU Tech Conference wrap-up. *HPCWire.* http://www.hpcwire.com/blogs/GPU-Tech-Conference-Wrap-Up-103679744.html

- Csongor, R. (September 23, 2010). NVIDIA GPU Technology Conference recap - day 2 by Rob Csongor. *LegitReviews.* http://www.legitreviews.com/news/9073/

- Staff. (September 22, 2010). Nvidia GPUs boost molecular biology research. *TG Daily.* http://www.tgdaily.com/general-sciences-features/51673-nvidia-gpus-boost-molecular-biology-research

- Staff. (September 22, 2010). GTC Day Two Keynote: Top computational biologist Dr. Klaus Schulten shows that seeing is believing. *CGSociety.* http://features.cgsociety.org/story.php?story_id=5876&referer=rss

- Kontzer, T. (September 22, 2010). GTC Day 2 Keynote: GPUs enabling molecular biology research. *NVIDIA Ntersect.* http://blogs.nvidia.com/ntersect/2010/09/gtc-day-2-keynote-gpus-enabling-molecular-biology-research.html?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+nvidia%2Fgtc+%28The+NVIDIA+Blog+-+GPU+Technology+Conference%29

- Staff. (September 15, 2010). NVIDIA GPU Technology Conference to focus on world's most important computing challenges. *MarketWatch.* http://www.marketwatch.com/story/nvidia-gpu-technology-conference-to-focus-on-worlds-most-important-computing-challenges-2010-09-15?reflink=MW_news_stmp

- Staff. (August 26, 2010). World-renowned robotics visionary and molecular-simulation pioneer to headline NVIDIA's 2010 GPU Technology Conference. *NVIDIA Press Release.* http://pressroom.nvidia.com/easyir/customrel.do?easyirid=A0D622CE9F579F09&version=live&releasejsp=release_157&prid=655694

  - Staff. (August 26, 2010). World-renowned robotics visionary and molecular-simulation pioneer to headline NVIDIA's 2010 GPU Technology Conference. *Marketwire.* http://www.marketwire.com/press-release/World-Renowned-Robotics-

Visionary-Molecular-Simulation-Pioneer-Headline-NVIDIAs-2010-NASDAQ-NVDA-1310006.htm

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- Staff. (August 18, 2010). GPGPU Personal supercomputer: Try before you buy. *indiaPRwire.* http://www.indiaprwire.com/pressrelease/computer-hardware/2010081859552.htm

- Dubrow, A. (July 19, 2010). New method could reduce cost of gene sequencing. *redOrbit.com.* http://www.redorbit.com/news/health/1893263/new_method_could_reduce_cost_of_gene_sequencing/

- Staff. (June 4, 2010). Atomic-scale model unravels ion channel gating. *Futurity.org.* http://futurity.org/top-stories/atomic-scale-model-unravels-ion-channel-gatin/

- Pappas, S. (April 29, 2010). 9 super-cool uses for supercomputers. *TechNewsDaily.com.* http://www.technewsdaily.com/9-super-cool-uses-for-supercomputers-0496/5

- Staff. (April 26, 2010). The molecular mechanics of hearing and deafness (w/video). *PhysOrg.com.* http://www.physorg.com/news191525518.html

- Staff. (April 20, 2010). TeraGrid resources help Harvard team gain insights into deafness. *HPCWire.* http://www.hpcwire.com/topic/applications/TeraGrid-Resources-Help-Harvard-Team-Gain-Insights-into-Deafness-91619564.html

- Dubrow, A. (April 19, 2010). Blueprint for the affordable genome. Ranger helps University of Illinois researchers simulate nanopore gene sequencer. *Texas Advanced Computing Center.* http://www.tacc.utexas.edu/news/feature-stories/2010/blueprint-for-the-affordable-genome/

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 26 Resource videos, with six new movies added during the period of April 2010 - March 2011. 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 2011, the most viewed movies were "Water Channels in Cell Membranes"[¶] with 20,746 views, "Six Microseconds of Protein Folding"[‖] with 18,767 views, and "Lipoproteins that Circulate in the Blood Collecting Fat"[**] with 16,679 views. The total count of all views of all listed videos since the gallery was started reached to around 85,378 views as of April 2011, representing 29,534 views over the April 2010 - March 2011 period.

[†] `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=AlfvWESPyZY`

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

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:

- Five week-long hands-on workshops on computational biophysics
- Nearly 97,000 views of all online tutorials
- Release of the *Forcing Substrates Through Channels* and *Timeline: a VMD Plugin for Trajectory Analysis* tutorials
- Updates to Resource tutorials
- Over 11,200 views of online case studies
- Twelve participants in the Resource's Visitor Program
- Doctoral and postdoctoral training
- Graduate and undergraduate classes taught by Resource faculty

Hands-on Workshops

From May 2010 - March 2011 the Resource organized five hands-on workshops in computational biophysics, held at extramural locations including Pittsburgh, San Diego, and Atlanta, as well as two local workshops held the Beckman Institute for Advanced Science and Technology in Urbana, 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:

- May 10–14, 2010 *Hands-on Workshop on Computational Biophysics at the Pittsburgh Supercomputing Center*[*] - sponsored by the National Resource for Biomedical Supercomputing[†] with some administrative and financial support from the Resource, and located at the Pittsburgh Supercomputing Center[‡], this workshop involved 30 participants from academia, including local and distant faculty, postdoctoral associates, and graduate students in the Resource curricula of lectures and tutorials. Evaluation results show that all participants agreed or strongly agreed that the workshop gave them new knowledge and insights, and that they felt their research would improve as a result.

- July 12–16, 2010 *Hands-on Workshop on Computational Biophysics at San Diego*[§] - with co-sponsorship from the National Biomedical Computational Resource (NBCR)[¶] and the National Resource for Automated Molecular Microscopy (NRAMM)[‖], 33 scholars from the west coast and institutes around the country and around the world participated in the workshop. Held at NRAMM site, and with publicity support from NBCR, the workshop program was expanded to include lectures by faculty affiliated with the sponsoring organizations. Evaluation results are positive, with 100% of participants indicating the workshop met their expectations, and that they would recommend the workshop to others.

- November 1–5, 2010 *Hands-on Workshop on Computational Biophysics at Urbana*[**] - at this workshop, 28 participants from as far away as Hawaii and New York attended the workshop, held at the home of the Resource on the University of Illinois campus. Workshop evaluation results are positive, with 100% of participants agreeing or strongly agreeing that the workshop improved their understanding of theoretical and computational biophysics, and with 95% agreeing or strongly agreeing that the workshop improved their ability of carry out original research in the area of theoretical and computational biophysics.

- November 29–December 3, 2010 *Hands-on Workshop on Computational Biophysics*

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[*] `http://www.ks.uiuc.edu/Training/Workshop/Pittsburgh_2010/`

[†] `http://www.nrbsc.org/`

[‡] `http://www.psc.edu/`

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

[¶] `http://www.nbcr.net/`

[‖] `http://nramm.scripps.edu/`

[**] `http://www.ks.uiuc.edu/Training/Workshop/Urbana_2010A/`

at Urbana[††] - the second workshop with dates in November 2010, at this event 31 scientists attending morning lectures and afternoon tutorials, and as was the case with the previous workshop, participants were invited to the office area of the Resource, and had the chance to interact with and learn from Resource scientists and software developers. Evaluation results are again positive, with 100% of participants indicating that the workshop met their expectations, and 96% indicating they would recommend the workshop to others.

- March 21-25, 2011 *Hands-on Workshop on Computational Biophysics at Atlanta*[†] - with co-sponsorship from multiple local organizations at the Georgia Institute of Technology (Integrative BioSystems Institute[‡], the Institute for Data and High Performance Computing[§], and the Parker H. Petit Institute for Bioengineering and Bioscience[¶]), the Resource held its largest event to date, providing lectures and tutorial to 51 academic and non-academic scientists from local institutions and from distant locales such as Turkey and Scotland. Results from evaluations found 97% of participants agreeing or strongly agreeing that the workshop improved their understanding of theoretical and computational biophysics, and that they would recommend the workshop to others.

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:

- *Forcing Substrates Through Channels* - in this tutorial, applications of steered molecular dynamics and adaptive biasing forces to the ammonium transporter AmtB are explored. Steered molecular dynamics is used first to gain an approximate knowledge of the permeation pathway and the barriers along it. Then, the

[††] `http://www.ks.uiuc.edu/Training/Workshop/Urbana_2010B/`

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

[‡] `http://www.ibsi.gatech.edu/`

[§] `http://www.hpc.gatech.edu/`

[¶] `http://www.ibb.gatech.edu/`

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

potential mean of force for ammonia in the central region of the channel is calculated using adaptive biasing forces. The appropriate choice of parameters and potential difficulties is also discussed.

- *Timeline: a VMD Plugin for Trajectory Analysis* - a tutorial for the Timeline plugin to VMD, which creates an interactive 2D box-plot – time vs. structural component – that can show detailed structural events of an entire system over an entire MD trajectory. Events in the trajectory appear as patterns in the 2D plot. The plugin provides several built-in analysis methods, and the means to define new analysis methods.

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 tutorial library, there were well over 96,500 views of all tutorials over the April 2010 - March 2011 period. The 10 most popular tutorials in terms of online views are shown in Table 3, with the tutorials providing introductions to VMD and NAMD the most popular.

Ten Most Viewed Tutorials	Views
VMD Tutorial	32,283
NAMD Tutorial (Unix/Mac)	12,973
VMD Images and Movies	7,504
NAMD Tutorial (Windows)	7,384
Membrane Proteins	4,406
Topology File Tutorial	3,289
Stretching Deca-Alanine	3,163
Adaptive Biasing Force Calculations	2,897
Building Gramicidin A	2,697
Alchemical Free Perturbation	2,671
Total for all tutorials	96,673

Table 3: Views of online tutorials from April 2010 - March 2011

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

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

web site. From April 2010 - March 2011 there were nearly 11,249 views of the case studies, with the *Myoglobin* and *DNA* case studies the most popular, as shown in Table 4.

Case Study	Views
Myoglobin	1,605
DNA	1,558
Ion Channels	1,483
Light Harvesting Complex II	1,469
Water and Ice	1,248
Membranes	896
Ubiquitin	892
BPTI	766
Titin Ig Domains	657
Aquaporins	675
Total	11,249

Table 4: Views of case studies from April 2010 - March 2011

Visitor Program

The Resource visitor program provides scientists (who typically come with their own financial support) with the opportunity to learn how to use Resource-produced software, other software hosted on Resource computers, and to benefit from the knowledge and expertise of Resource members. Resource members spend substantial amounts of time helping visitors achieve their educational and research goals. At the end of their time at the Resource, visitors acquired critical skills and new experiences that they took back to their home laboratories. Visits may last for several days to several months. Visitors to the Resource during the May 2010 - April 2011 period (listed by the month(s) of their visit) include:

- Axel Bidon-Chanal, University Henri-Poincare, France (July 2010)
- Saikat Chowdhury, The Pennsylvania State University (March - April, 2010)
- Jonathan Lai, New York University (June 2010)
- Ly Le, Ho Chi Minh International University (September 2010)
- Paul McCreary, Evergreen State College (August - September 2010)
- Maria Musgaard, Aarhus University, Denmark (March - July 2010)

- Ken Olsen, Loyola University (September - December 2010)
- Ilia Solov'yov, Johann Wolfgang Goethe University, Germany (July - August 2010)
- Sebastian Stolzenberg, Cornell Medical College (April 2010)
- Ioan Vancea, Forschungszentrum Juelich, Germany (May 2010)
- Lei Wang, University of Science and Technology, China (November 2009 - October 2010)
- Jaie Woodard, Oberlin University (June - August 2010)

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.

- Fatemeh Khalili Araghi, Physics, University of Illinois, Fall 2010
- Jen Hsin, Physics, University of Illinois, Fall 2010

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

- James Gumbart
- Wei Han
- David Hardy
- Chris Harrison
- Barry Isralewitz
- Fatemeh Khalili Araghi
- Eric Lee
- Eduard Schreiner
- Melih Sener
- Amy Shih

- Ilia Solov'yov
- 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 2010 - Spring 2011 are listed below.

- Advanced Statistical Mechanics
- Biomolecular Physics
- Statistical Thermodynamics
- Molecular and Cell Biology
- University Physics: Mechanics
- University Physics: Electricity & Magnetism
- Nonequilibrium Statistical Mechanics

Resource Library

The Resource library, an important internal training resource, has been expanded by the purchase of 20 new books, bringing the total volume count to 1,082 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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