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Contents

The preparation of this report was coordinated by Tim Skirvin

Subprojects

BTA UNIT: C

TITLE: Molecular Basis of Hearing

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% BTA $: 3%

ABSTRACT: The vertebrate sense of hearing employs mechanically sensitive hair cells to transform complex mechanical stimuli produced by sound into electrical signals. The microscopic structures involved are well understood: Stereocilia in each hair cell bundle are arranged in rows of increasing height, and a fine filament, termed the 'tip link', connects the tip of each stereocilium to the side of its taller neighbor. Tip links are thought to connect directly to transduction channels, so that deflections of a hair bundle —that would tighten tip links— open these channels.

In recent years, proteins making up the transduction apparatus have begun to be identified. The tip link is composed in large part of cadherin 23 [1–3], whereas the transduction channel is likely formed by subunits of the TRP channel family containing multiple ankyrin repeats in their cytoplasmic termini [4–8]. The challenge at this point is to correlate the experimentally determined properties of the transduction apparatus with the proteins it comprises.

An important step in characterizing the elastic behavior of cadherin and ankyrin has already been accomplished and reported in a joint publication with our collaborator [9]*. Several systems containing up to 340,000 atoms were investigated involving multiple multi-nanosecond simulations performed with NAMD on the NSF supercomputing centers. Following earlier work [10], the Resource carried out multiple

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

SMD simulations that determined the elastic properties of cadherin. The results indicated that this protein is likely a stiff element that responds to an external force by independently unfolding its two β-sheets. The force required to unfold these domains was found to depend on the presence or absence of Ca^{2+} ions, pointing out the role of calcium and conserved residues as structural stabilizers. In the same report [9] the elastic properties of ankyrin repeats were extensively investigated. Large stacks of ankyrin repeats were found to reversibly elongate through changes in curvature while keeping their secondary structure intact (Fig. 1 D). Moreover, computed elastic moduli and working extension of ankyrin match the properties of an experimentally-defined elastic element called "the gating spring" [3, 11–13]. Along with available experimental data, the simulations helped to develop an overall picture of the mechanotransduction process in which ankyrin repeats in the transduction channel, rather than the tip link, act as the gating spring [3, 9]. The simulations carried out by the Resource also revealed that, besides being a suitable candidate for the gating spring, ankyrin may protect the transduction apparatus against extreme stimuli by further unfolding of its individual repeats. Future studies will focus on the temperature and salt concentration dependence of ankyrin elasticity, as well as on how particular mutations related to hereditary diseases affect ankyrin and cadherin causing deafness.

BTA UNIT: C

TITLE: Substrate permeation and selectivity in aquaporins

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ABSTRACT: Permeation of water across cellular membranes is facilitated by a family of transmembrane channels called Aquaporins (AQPs)* [14, 15,]. These selective channels are present in all forms of life, including mammals, amphibia, insects, plants, and bacteria [15–17,]. In human, eleven different AQPs have been characterized in various organs such as kidneys, eyes, and the brain. AQPs are fundamental to osmoregulation of a large variety of cells [16,]. Impaired function of AQPs has been associated with diseases like nephrogenic diabetes insipidus and congenital cataract [15, 16, 18, 19,].

The recent availability of high-resolution structures of two structurally highly homologous, but functionally distinct AQPs from the same species, namely *E. coli* AqpZ [20], a pure water channel, and GlpF [21], which also conducts glycerol, presented a unique opportunity to develop an understanding for the structural basis underlying substrate selectivity in these channels. Using molecular dynamics simulations [22], the free energy profile of glycerol conduction through AqpZ was calculated and compared with that in GlpF, revealing a much larger barrier in AqpZ (22.8 kcal/mol) than in GlpF (7.3 kcal/mol). In either channel the highest barrier is located at the selectivity filter. Analysis of trajectories and substrate-protein interactions suggests that steric restriction of AqpZ is the main contribution to this large barrier. Another important difference is the presence of a deep energy well at the periplasmic vestibule of GlpF, which was not found in AqpZ. The latter difference can be attributed to the more pronounced structural asymmetry of GlpF, which may play a role in the ability of the protein to attract glycerol.

We have also developed a new computational model to describe water permeation through AQPs as well as any other channels by a single collective coordinate. A collective diffusion model is proposed in which water movement at equilibrium is characterized as an unbiased diffusion along this coordinate and water transport in the presence of a chemical potential difference is described as one-dimensional diffusion in a linear potential. The model allows one to determine the osmotic permeability of water channels from equilibrium simulations [23, 24].

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

BTA UNIT: C

TITLE: Chemomechanical energy coupling in F1-ATP Synthase

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ABSTRACT: Every day, the human body synthesizes up to its own body weight in the molecule adenosine tri-phosphate (ATP), the cellular energy currency. This chemical reaction is catalyzed by the enzyme ATP synthase, inside the F1 part of the protein. F1-ATPase, by itself, is a molecular motor that can use the energy stored in ATP to generate mechanical rotation. F1 consists of a hexameric arrangement of alpha and beta subunits that accommodate the three catalytic binding sites and a central stalk carrying out the mechanical rotation.

The Resource has investigated the mechanical coupling of central stalk rotation to synthesis/hydrolysis in F1-ATPase via two methods: equilibration of components of the system, and SMD simulations on a stalk/single-beta system. The component equilibration examined the tendency towards spontaneous conformational change of isolated open, half-closed, and closed beta subunits of F1. All subunits demonstrated a tendency to move toward a common overall conformation, via two different motions: one parallel to the pseudo-symmetry axis of F1 and one perpendicular to this axis. The SMD simulations used a novel harmonic restraint protocol to examine the behavior of the central stalk when a beta subunit is forced to close, simulating F1 functioning in hydrolysis mode. In a model system consisting of the central stalk and a single beta subunit, steered molecular dynamics transforms the beta subunit from an open state to a closed state, while the central stalk is constrained to rotate on the pseudo-symmetry axis. The results underlined the importance of the 2-part closing paths observed in the equilibrations: a simple closing path causes the stalk to rotate in the wrong direction.

Furthermore, the Resource has analyzed the catalysis of ATP hydrolysis and its coupling to stalk rotation in the catalytic binding pockets of F1-ATPase. Combined quantum mechanical/molecular mechanical simulations employing density functional theory were used in two catalytic binding pockets to investigate the hydrolysis reaction pathways, their energetics, and the coupling of the chemical reaction to conformational changes of the protein environment [25, 26]. Efficient ATP hydrolysis was found to proceed via a novel proton-relay mechanism involving two water molecules stressing the importance of the protein environment in pre-organizing the solvent environment around the nucleotide. Energetically, the catalytic reaction was found to be significantly different between both binding pockets: strongly endothermic in one and approximately equi-energetic in the other. Additional computational mutation studies revealed that movement of an “arginine finger” residue was largely responsible for this difference, thereby, controlling the energetics of the catalytic event. This arginine residue was therefore proposed to be of major importance for mediating communication among subunits of F1 to achieve the catalytic cooperativity observed in experiments.

BTA UNIT: T

TITLE: Gas Transport Pathways in Hydrogenase

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ABSTRACT: [Fe]-hygrogenases are found in a wide variety of unicellular organisms and are generally involved in H_2 production. This property of hygrogenases offers the promise of affordable large-scale production of H_2 as a source of renewable energy. An important part of their function is related to internal gas-transport (they produce H_2 and are deactivated by O_2), which until now was poorly understood.

Molecular dynamics simulations of a fully-hydrated 60,000 atoms system of CpI hydrogenase from *Clostridium pasteurianum* performed by NAMD [27], have revealed the gas pathways and diffusion mechanisms of O_2 and H_2 inside hydrogenase [28–30]. The Resource developed two new methodologies for studying gas access and applied it to the case of hydrogenase: (1) temperature-controlled locally enhanced sampling, and (2) volumetric solvent accessibility maps, both methods providing consistent results. Both methodologies confirm the existence and function of a previously hypothesized pathway and reveal a second major gas pathway which had not been detected by previous analyses of CpI (our method is the first to ever claim to be able to find all gas pathways in a protein). Two completely different modes of intra-protein transport were found for H_2 and O_2, which in the model are differentiated only by their size. Furthermore, the Resource found strong evidence that supports the hypothesis that small hydrophobic molecules diffusing inside proteins take advantage of pre-existing dynamical packing defects which are not visible in the protein's static structure, but may be easily predicted from the protein's equilibrium dynamics. The methods developed are easily applicable to any protein capable of gas transport and storage, such as myoglobins and oxygenases for example.

BTA UNIT: C

TITLE: Mechanical properties of fibronectin and integrin

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ABSTRACT: Cells are glued to their surroundings through a family of transmembrane receptor proteins known as integrins. The growth, movement and survival of cells are all dependent on bidirectional signals relayed by integrins across the cell membrane [31]. Each integrin consists of two non-covalently associated heterogeneous subunits: α and β. In mammalian cells, eighteen α and eight β subunits form 24 different types of integrins, the extracellular heads of which selectively bind to extracellular matrix proteins such as collagen, fibronectin, or a few cell surface adhesion proteins. The intracellular tails of integrins are mechanically coupled to the cytoskeleton, which exerts force stretching the integrins. By forming a stable mechanical linkage an integrin-ligand complex conveys mechanical force signals across the membrane.

Recent crystal structures of integrin $\alpha_V\beta_3$ in complex with a mimetic ligand provide a structural basis how this integrin interacts with its ligand [32]. The ligand-binding to the integrin does not involve a deep binding pocket that protects force-bearing contacts from attacks by free water but forms a shallow crevice at the interface between the two subunits. One divalent metal ion acquired by the β_3 subunit binds to the ligand. To understand how this complex resists the mechanical force by using the divalent ion, we performed SMD simulations to investigate the mechanical properties of the complex [33]. The simulations revealed that the complex is stabilized from detachment by a single water molecule that is tightly coordinated to the ion, thereby blocking access of free water molecules to the critical force bearing interactions. The structural motif coordinating the metal ion is common to many proteins that contain the phylogenetically ancient von Willebrand A (vWA) domain, including integrins, the anthrax toxin receptor, various calcium and chloride channels, complement factors, protease inhibitors, as well as the family of vWA collagens. The functional role of single water molecules tightly coordinated to the MIDAS ion observed in the present study might be a more general principle of how divalent cations stabilize protein-protein interactions against cell derived forces.

Integrins exhibit large conformational changes during the activation. To derive high-resolution structural insights into how mechanical force may induce the conformational changes, we docked a physiological ligand, a fibronectin type III module FN-III$_{10}$, to the headpiece of integrin $\alpha_V\beta_3$, and extended the SMD study to stretch the ligand under various configurations [34]. Starting with the hydrated "closed" crystal structure of the complex, we show that mechanical force can switch the integrin headpiece to the "open" state. This force-regulated opening is characterized by an increase in the hinge angle between the two β head domains that is made possible by the breakage of a highly conserved hydrogen bond. The open conformation derived here overlays closely with the recently published open liganded integrin $\alpha_{IIb}\beta_3$ crystal structure [35]. The direction along which the force is transmitted through the integrin is critical for its activation. The integrin headpiece opens only if the force is transmitted through the divalent ion along the β subunit.

BTA UNIT: T

TITLE: Lac Repressor-DNA loop dynamics

KEYWORDS:

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ABSTRACT: ABSTRACT

Protein-DNA interaction arises in many different contexts in the cell. A particularly relevant case involves the core process of life, the expression of genetic information, in which proteins regulate transcription by manipulating the structure of DNA. The *lac* repressor protein is a classical protein of this kind. It binds two DNA sites and induces a loop with the intervening DNA, inhibiting the expression of three genes that code for proteins involved in lactose digestion in *E. coli*. This protein is the simplest genetic switch known, and has been studied extensively for the past 50 years, yet the mechanics of repression are still not understood. The system presents an ideal scenario for the study of the general principles underlying structural dynamics of proteins that regulate DNA.

Generally, the sizes of biomolecules and time scale of events involved in protein-DNA interactions span several orders of magnitude, calling for a multiscale approach. The

resource developed one such method for modeling protein-DNA complexes [36]* that combines two levels of description: the elastic rod model is used to build the equilibrium structure of the DNA loop [37], and MD is used to simulate the dynamics of the protein. The structure obtained from the MD simulations provides the boundary conditions for the elastic rod calculation. The forces and torques that the loop would exert on the protein are obtained from the rod calculation and included in the MD simulation using the Steered Molecular Dynamics approach [38]. For the all-atom MD simulations, a structure of the *lac* repressor bound to two short pieces of DNA was constructed by combining several NMR and crystal structures and equilibrated [39]. However, none of the available structures contained the DNA loop induced by the protein. The structure of the loop was predicted using the coarse-grained model [40]. Multiscale simulations were performed to observe the response of the protein to the strain induced by the DNA loop [41]. The simulations revealed large scale motions of the protein in response to the strain. Different domains of the protein showed remarkable stability, conserving the structure throughout the simulation and moving with respect to each other much like rigid bodies. The principal degrees of freedom of the protein are limited to the DNA binding domains, that can absorb all the strain of the DNA without disrupting the overall structure of the protein. The simulations suggest that the stability of the core of the protein, necessary for efficient repression, is due to a group of residues, which form a "lock" mechanism that keeps the protein in a closed configuration. The study throws light onto much needed detail of the underlying principles of the design of the protein, which will help in the understanding and design of other gene control systems.

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

BTA UNIT: C

TITLE: Light induced signaling in LOV domains

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ABSTRACT: ABSTRACT

The Light, Oxygen, and Voltage (LOV) sensitive domains are photoreceptors found in plant phototropins. Phototropins are proteins crucial for the life cycle of most photosynthetic organisms and are responsible for the regulation of phototropism, stomatal opening and closing, chloroplast relocation, and gametogenesis. Blue-light absorption in LOV by the chromophore FMN leads to the formation of a covalent flavin-cysteinyl adduct state between the protein and FMN that eventually triggers the activity of an attached serine-threonine kinase domain. Recently, X-ray structures of several photoreaction intermediates of LOV domains have been determined at high resolution.

The Resource has used two complementary approaches to examine photoexcitation and signaling in LOV domains. Combined quantum mechanical/molecular mechanical (QM/MM) simulations at the B3LYP/6-31G* and HF/6-31G(2p,2d) level of theory were used to investigate the elementary steps in the photocycle of LOV [42]. The system is comprised of nearly 20,000 atoms in the MM segment and 37 quantum mechanically treated atoms. The Resource investigated the singlet ground state, several excited triplet state intermediates, as well as the singlet flavin-cysteinyl adduct state. Several proposals regarding the pathway of adduct formation in the triplet state have been put forward based on experimental data.

The QM/MM simulation results clearly revealed a neutral triplet radical state as the physically relevant gateway to adduct formation. Further analysis of the electronic wavefunction of the triplet radical state also revealed a possible mechanism for efficient intersystem crossing from the triplet to the singlet state, thereby, explaining why the neutral radical species has so far eluded experimental study.

In a second approach the Resource has used NAMD2 to conduct MD simulations to investigate the dynamical behavior of LOV domains in their inactivated dark and activated light state. Structurally, the dark and light states are found to be very similar based on X-ray crystallography data, giving rise to the question of how signaling occurs after photoexcitation has taken place. The Resource has conducted multiple sets of MD simulations for both the dark and light states and found a significant difference in the dynamical behavior of a region in LOV that contains a key salt bridge. It was found that in the dark state this salt bridge is formed only about 22% of the time, whereas it is present more than 70% of the time in the light state. It is therefore proposed that this region is of key significance for the signaling mechanism.

BTA UNIT: C

TITLE: Mechanosensitive Ion Channels

KEYWORDS:

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ABSTRACT: Mechanosensitive channels constitute a class of ubiquitous membrane proteins [43] that mediate the stimulation of exocytosis under mechanical strain [44,45], and play important roles in hearing, touch, and cardiovascular regulation [46]. In bacteria, MS channels are crucial for protecting the cell from osmotic shock and for regulation of its volume.

Crystal structures of two MS channels have been solved: the closed form of the MS channel of large conductance (MscL) from *M. tuberculosis* [47] and the putative open form of the Mechanosensitive Channel of Small Conductance (MscS) from *E. coli* [48]. Both channels are activated by mechanical stress in the cell membrane, providing a controlled response to the osmotic pressure of the environment.

Although the crystal structure of MscS gave a detailed view of its molecular architecture, and new experimental results [49–51] are shedding light on MscS function, key questions remain unanswered. Is MscS only a safety valve? What residues are relevant for MscS gating? Is the crystal structure conformation really open? How does the closed state of MscS look like? What is the role of the large MscS cytoplasmic domain?

Several multi-nanosecond, all-atom, molecular dynamics simulations were carried out by the Resource to explore the dynamics of MscS in its native environment (protein, lipid bilayer, water, and ions: 224,000 atom system) as reported in [52]. The simulations revealed that restraints on the backbone of the protein kept the open form and allowed intermittent permeation of water molecules through the channel. Abolishing the restraints under constant pressure conditions led to spontaneous closure of the transmembrane channel, whereas abolishing the restraints when surface tension (20 dyn/cm) was applied led to channel widening. The simulations also showed spontaneous diffusion of ions through the side openings of the large cytoplasmic domain of MscS, formation of salt bridges that may be essential for gating of MscS, and a distinctively different distribution of positive and negative ions in and around the channel.

The conduction of ions through the MscS channel is now being studied utilizing a multi-scale approach in which different conformations of the channel resulting from SMD simulations are probed with a Boltzmann transport Monte Carlo method [53]. In addition, the accessibility of individual residues of MscS conformations characterized through computational methods are being compared to data obtained from EPR experiments performed by our collaborator, Eduardo A. Perozo.

BTA UNIT: C

TITLE: Nanodisc

KEYWORDS:

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ABSTRACT: ABSTRACT

Human apolipoprotein A-1 (apo A-1) is the major protein component of high density lipoproteins (HDL), which are involved in transporting cholesterol from tissues and organs to the liver for degradation. The transport of cholesterol is important since high levels of cholesterol in the blood can lead to a hardening of the arteries (artherosclerosis), heart disease and stroke. Based on previous secondary structure predictions, apo A-1 was proposed to have a 43 residue N-terminal globular domain and a 200-residue C-terminal lipid-binding domain. The X-ray crystal structure of a lipid-free 200-residue apo A-1 lipid binding domain has been determined, but the structure of the protein bound to lipid remains unknown. The most widely accepted model for how the apo A-1 surrounds the lipid bilayer suggests a double-belt model in which two apo A-1 proteins wrap around the lipid bilayer in an anti-parallel belt-like fashion. We used the apo A-1 lipid-binding domain as a template for the synthesis of amphipathic helical proteins termed membrane scaffold proteins, employed to self-assemble soluble monodisperse discoidal particles called Nanodiscs. In these particles, membrane scaffold proteins surround a lipid bilayer forming bilayer discs of discrete size and composition.

We investigated the structure of Nanodiscs through molecular dynamics simulations in which Nanodiscs were built from scaffold proteins of various lengths [54]. Using

NAMD, molecular dynamics simulations were performed on several Nanodiscs prepared with scaffold proteins containing the full predicted 200-residue lipid-binding domain as well as two truncated versions in which the first 11 or 22 N-terminal residues were removed. These simulations consisted of between 140,000 to 150,000 atoms each and were run from between 4.5 and 6.9 ns. The simulations showed planar or deformed Nanodiscs depending on optimal length and alignment of the scaffold proteins. Based on mean surface area per lipid calculations, comparison of small angle x-ray scattering curves, and the relatively planar shape of Nanodiscs made from truncated scaffold proteins, one can conclude that the first 17 to 18 residues of the 200-residue apo A-1 lipid binding domain are not involved in formation of the protein belts surrounding the lipid bilayer.

BTA UNIT: C

TITLE: Sequencing DNA with a nanopore device

KEYWORDS:

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ABSTRACT: An electronic device for reading the genetic information encoded in DNA can be built around a tiny pore in a thin (2-5 nm) silicon membrane. The chemical sequence of a DNA strand could be discerned by such a device, in principle, through a semiconductor detector integrated with the pore that would record the electrical signal induced by the DNA molecule transiting the pore. To complement ongoing experimental studies developing such pores and measuring signals in response to the presence of DNA (Gregory Timp, UIUC), the Resource has been conducting MD simulations of DNA translocation through synthetic nanopores*.

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

In order to achieve the goal of sequencing, microscopic conformations of DNA inside synthetic nanopores have to be related to the measured electric signatures. The Resource has pioneered the methodology for microscopic simulation of nanopore systems comprising of DNA and a synthetic membrane [55]. We have demonstrated through MD simulations [55–58] that measured electric signatures can be related to microscopic conformations of DNA. Unique features of the NAMD2 program [59] allowed the Resource to carry out high-performance simulations of such unusual systems accounting for up to 200,000 atoms.

The results suggest that the rate-limiting step for the DNA translocation is not the actual transit of DNA through the pore, but rather the search for an initial conformation that facilitates the translocation. Current blockades induced by DNA occluding the pore mouth, but not transiting the pore, were found to have the same magnitude as the blockade observed when DNA transits the pore. Hydrophobic interactions between DNA bases and the pore surface can slow down translocation of single stranded DNA and might favor unzipping of double stranded DNA inside the pore. Translocation of double stranded DNA (dsDNA) is conditioned by both the diameter of the pore and the applied transmembrane bias. Pores wider than 2.5 nm in diameter allow dsDNA to pass through at low transmembrane biases (<200 mV). Pores that are 1.4 to 2.5 nm in diameter can conduct dsDNA if the magnitude of the applied bias is sufficiently high to stretch the double helix, reducing its diameter. Pores smaller than 1.4 nm in diameter cannot admit dsDNA; single DNA strand were observed to translocation through 1.0-nm-diameter and wider pores. Two papers describing these studies were published last year [55, 56], two more have been submitted for publication [57, 58].

BTA UNIT: T

TITLE: Empirical Nanotube Model for Biological Applications

KEYWORDS:

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% BTA $: 3 %

ABSTRACT: Single-walled carbon nanotubes (SWNTs) are hollow cylinders made from single graphite layers [60]. They are typically a few nanometers in diameter and several microns long. Due to their superb electronic properties, mechanical strength and chemical stability, SWNTs become building blocks of nanotechnology and hold great promise for applications in biomedicine and biotechnology. For example, the nano-sized pore can be utilized as molecular channels to conduct water [61], protons [62], polymers [63], and nucleic acids [64]. Knowledge of channel transport mechanisms helps people to understand nano fluidics, and may contribute to desalination of sea water [65]. In addition, the optical signals of the SWNTs are sensitive to the

environment. Tracing the change in the optical signals allows the detection of the biomolecules with high sensitivity, which qualifies nanotubes as bio-sensors [66].

For such applications, it is crucial to understand the interaction of SWNTs and water and/or other biomolecules in the aqueous environment. A major challenge in such investigations is to treat the delocalized π-electrons of SWNTs accurately and efficiently, which is likely to be a critical factor affecting transport dynamics. The Resource has developed a semi-empirical method [67] to address this issue. The electronic energy spectrum and screening constants computed with this approach agree well with results from first principle calculations, but the new approach is computationally much more efficient [68, 69]. To improve the quality of electrostatics in the existing MD force fields, the Resource parameterized the atomic partial charges of SWNTs through density functional theory calculations. For a realistic application, the new method is employed to study water transport through a 1.4 nm long SWNT channel. The atomic partial charges on the nanotube edges are found to greatly contribute to the total interaction energy and may influence the water entering, while the polarization of the SWNT significantly lowers the electrostatic energy in the tube center [69]. The Resource is making efforts to implement the semi-empirical model into NAMD [27] so that the electronic response of SWNTs can be evaluated on-the-fly during molecular dynamics simulations.

BTA UNIT: C

TITLE: Excitation transfer dynamics in trimeric photosystem I

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% BTA $: 4 %

ABSTRACT: ABSTRACT *

Photosystem I (PSI) is one of the two major light-harvesting complexes utilized by oxygenic photosynthetic organisms, such as cyanobacteria, green algae, or higher plants [70–72]. PSI converts the electronic excitation energy resulting from the absorption of a photon by its pigment antenna array into a charge gradient across the membrane, which is later utilized by the enzyme F-ATPase for ATP synthesis. This mechanism, by which incident light energy is stored in progressively more stable forms, is the main source of energy for almost all the biosphere [73, 74].

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

With the recent availability of crystal structures for photosystem I (PSI) in cyanobacteria and plants, it is possible for the first time to compare the excitation transfer networks in this highly ubiquitous light harvesting complex from two domains of life. The Resource used structure-based modeling methods to examine in detail the excitation transfer kinetics of the plant PSI-LHCI supercomplex. For this purpose an effective Hamiltonian was constructed for plant PSI that combines an existing cyanobacterial model for structurally conserved chlorophylls with spectral information for nonconserved chlorophylls. The plant PSI excitation migration network thus characterized was compared with the cyanobacterial system investigated in a recent study by the Resource [75]. An efficient coupling is observed between the peripheral Lhca subunits and the PSI-core in plants. The role of gap chlorophylls in facilitating this efficient coupling was examined. It was also investigated whether the particular arrangement of non-conserved chlorophylls in the PSI-LHCI supercomplex optimizes either light-harvesting efficiency or the connectivity of the outer pigment array to the PSI core. No signs of such incremental optimality in the outer pigment cluster was observed in relation to the excitation transfer process. This lead to the conclusion that PSI must have experienced stronger constraints than the quantum yield of the excitation transfer process during over one billion years of divergent evolution separating cyanobacteria and plants. A paper describing this study has been submitted to the Biophysical Journal.

BTA UNIT: T

TITLE: Fast Methods for Electrostatics and Polarization

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% BTA $: 3%

ABSTRACT: NAMD [27] uses the particle–mesh–Ewald (PME) method [76] to compute electrostatics for periodic simulations, but currently NAMD lacks a fast algorithm for nonperiodic systems. Work is ongoing to develop a fast electrostatics method based on a hierarchical interpolation of softened pairwise potentials on multiple grids [77,78]. Tests show that, compared to the fast multipole algorithm, this *multilevel summation method** is ten times faster when used with error tolerances appropriate for molecular dynamics. This method has also been implemented for Ewald periodic boundary conditions and demonstrated to be competitive with PME. Recent development shows that using higher degree polynomial interpolation can increase the accuracy of the method significantly and make it comparable to the accuracy level of the PME method. A parallel implementation of the multilevel summation method is being developed for the next version of NAMD to provide fast electrostatics for nonperiodic systems and a more scalable alternative for periodic systems.

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

The inclusion of electronic polarizability is considered the single most desirable improvement [79–81] in the next generation force fields, but the high computational cost has impeded development. In particular, the cost in [82] is close to 8 work units, where 1 work unit is the computational cost for a non-polarizable force evaluation. The goal of the second part of this subproject is to reduce the cost of computing polarizability to make it more useful for molecular dynamics. The self-consistent implementation of the point dipole model has been chosen because it is more reliable than the extended Lagrangian method, is applicable to kinetic as well as thermodynamic calculations, and provides a standard against which other approximation approaches can be compared. Algorithms for a self-consistent calculation have been constructed that reduce the computational cost to less than 2 work units, making it feasible to use polarizable force fields in molecular dynamics simulations. Software has been written and tested using an existing sequential molecular dynamics program so that it will be straightforward to incorporate polarizable force fields into the next version of NAMD.

BTA UNIT: T

TITLE: BioCoRE

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% BTA $: 12%

ABSTRACT: BioCoRE [83] is a web-based collaborative environment designed to enhance biomedical research and training.* By using a standard web-browser (on a desktop or laptop computer or handheld PDA) scientists create projects in which all private data is secure and is shared only within the specific project team. Researchers use BioCoRE to create input files for supercomputer runs, submit jobs to remote sites including supercomputers, and share the visualization of molecular systems across distances. BioCoRE features a synchronous and asynchronous chat, a project-wide "bookmarks" file for sharing web links, as well as a web-based filesystem. Summary pages within BioCoRE regularly inform the project team of the project status. BioCoRE sessions are automatically recorded and can be reviewed later by all project team members. A built-in evaluation component provides systematic and continuous user feedback.

Major BioCoRE developments in the past year include the public release of a new interface to the environment, as well as new tools for researchers.

The new BioCoRE interface has been designed to be more efficient for the researchers as well as conform to the latest web standards. Along with the new release, a collection of new tools have been released to enhance the research process. Among these tools is the ability to have BioCoRE send email to a user's email account when important events occur within a project that they are watching. For instance, a user might wish to be informed when new files are added to a particular folder within the BioFS, or when new states are published via VMD. The BioCoRE filesystem, BioFS, has seen a marked increase in usage over the past year, and WebDAV [84] access has been largely rewritten to make it more robust.

To serve teaching and education, a poll/quiz module has been added to BioCoRE. An administrator of a project can pose questions to project members which show up via their Control Panel. The administrator can choose when the poll or quiz should start and end, as well as whether or not the answers should be multiple choice or fill in the blank.

Future BioCoRE efforts will focus on additional integration of biomedical applications, further development of the training arena, and on increased adoption of BioCoRE by the community.

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

BTA UNIT: T

TITLE: VMD

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% BTA $: 10 %

ABSTRACT: VMD [85] is a molecular visualization program that provides interactive biomolecular display and analysis capabilities. VMD incorporates built-in scripting features for user extensibility and automation of complex visualization and analysis.*

VMD runs on all major operating systems and supports computers ranging from laptops to graphics supercomputers, allowing it to scale with varying problem size. 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 language, and 64-bit processors.

In the past year, VMD has been extended with new features for aligning multiple structures and their respective sequences, a new high-quality secondary structure representation, high-quality interactive ray tracing of VDW sphere representations and transparency using OpenGL programmable shading on the graphics processor, and a new 3-D texturing feature which allows molecular structure representations to be colored by volumetric properties such as electrostatic potential. Significant improvements have been made to the speed and quality of molecular renderings produced VMD, and in particular with the use of external ray tracing packages such as Tachyon, and POV-Ray. New plugins have been developed, adding support for several new molecular and volumetric file formats.

More than 11,000 new users registered and downloaded VMD 1.8.2 since the previous progress report. The latest version, VMD 1.8.3, was just recently released on February 15, 2005. As of May 20, 2005, over 6,900 unique users had registered and downloaded this newest version. A set of new and updated plugins was released for VMD 1.8.3 on May 12, 2005.

Ongoing VMD developments include additional multiple sequence alignment capabilities, improved centering and viewing controls, more flexible movie and presentation preparation tools, and continued progress towards multiple simultaneous structure views in a single VMD session. The next release of VMD, version 1.8.4 is planned for the summer of 2005.

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

BTA UNIT: T

TITLE: MultiSeq: A VMD Multiple Alignment Plug-in

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% BTA $: 5%

ABSTRACT: MultiSeq* is a tcl-scripted plug-in for VMD version 1.8.3 that runs on all major operating systems and allows for the comparison and evolutionary analysis of multiple structures and sequences within VMD. Structures are aligned with the STAMP program [86], which uses an iterative dynamic programming algorithm and is written in C. To handle the problem of redundant data in building profiles for a set homologous proteins, MultiSeq employs a multidimensional QR factorization of the alignment to provide a maximally independent set of proteins that best represent the topology of the phylogenetic tree for the homologous group of proteins [87]. Phylogenetic trees, which are based on the agglomerative UPGMA algorithm and a choice among several structural metrics, are displayed and labeled by domain of life, organism name, and pdb code. Regions of either sequence and structure conservation can be mapped directly onto the overlapped structures using a variety of graphical representations. The alignments and secondary structure information can be output in FASTA format.

The current released version of MultiSeq focuses primarily on structural data. The next release, however, will provide an environment in which information from both multiple sequences, including those without known structures, and multiple structures can be combined in a unified treatment. As many of the algorithms involve manipulations that are independent of the data type, e.g., sequence or structure, a bioinformatics toolkit has been created that provides programming modules commonly used by different functions within MultiSeq. This C++ based library allows for efficient execution of computationally intensive algorithms within the VMD plug-in framework, reuse of core software constructs, and also allows standalone versions of the algorithms to be created with little effort†. For example, although different orthogonal encodings are used to handle sequence and structural data sets, the algorithmic logic of the multidimensional QR algorithm is nearly the same in both cases [88]. The next release, which is near completion, provides alignment and evolutionary analysis tools for independent sets of multiple sequence and structure data. By combining both sequence and structure information, complete evolutionary profiles for database searches, genome annotation, and other comparative studies will be possible.

In addition to allowing the user to modify the sequence and structure alignments, MultiSeq now contains a sequence editor. The Resource has been discussing with Professor Carl Woese in the Microbiology Department at UIUC to develop an intuitive interface for the sequence editor and other features that are useful for experimentalists and theoreticians working in both the sequence and structure worlds

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

†URL: `http://www.scs.uiuc.edu/ schulten/software.html`

of molecular biology. New and exciting features scheduled for future inclusion include tools for multiple sequence and profile alignment, constructing sequence-based phylogenies, covariance analysis and the incorporation of secondary structure information into the alignment process.

BTA UNIT: T

TITLE: NAMD: Scalable Molecular Dynamics Software

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% BTA $: 10%

ABSTRACT: NAMD* is a parallel molecular dynamics code designed for high performance simulation of large biomolecular systems [27]. NAMD employs the prioritized message-driven execution capabilities of the Charm++/Converse parallel runtime system,† allowing excellent parallel scaling on both massively parallel supercomputers and commodity workstation clusters. NAMD is distributed free of charge to over 12,000 registered users as both source code and convenient precompiled binaries. A publication in press [89] documents the current capabilities, algorithms, and design of NAMD and provides examples of applications ranging from a tutorial exercise to the large multiscale simulation of [41].

Prior investments in serial performance tuning on the Itanium processor bore fruit yet again as NAMD was rapidly ported to the SGI Altix at the National Center for Supercomputing Applications (NCSA). This new machine immediately became the platform of choice for NAMD users at the Resource, providing serial performance 80% better than NCSA's Xeon cluster and 22% better than the fastest TeraGrid cluster despite only a 7% difference in clock speed. Parallel efficiency is 80% on 128 CPUs for the standard NAMD benchmark, and should improve with tuning. The Altix is ideal for interactive MD, both because of its performance and because it is a large shared-memory machine on which long-running jobs could be suspended when processors are needed for interactive simulations. This type of "on-demand" usage has been available on the Resource clusters for several years, but the Altix both doubles the performance of IMD and is available outside of the Resource.

NAMD has also been ported to a 640-node Apple Xserve G5 cluster and to an Opteron/Infiniband cluster, both at Illinois. NAMD 2.6, supporting these new platforms and incorporating the improvements in version 5.9 of the Charm parallel runtime, will be released in June 2005. The Resource has begun collaborations with NCSA and Prof. Wen-mei Hwu, Electrical and Computer Engineering, Illinois, to implement the dominant NAMD routines on field-programmable gate arrays (FPGAs), an application acceleration technology available on the Cray XD1 and, soon, the SGI Altix. A similar project with the Resource will implement these same routines on modern programmable graphics accelerators, leveraging experience from the molecular graphics program VMD. The new Opteron-based Cray XT3 at the Pittsburgh Supercomputing Center remains unavailable to us due to vendor restrictions, but will be the primary porting and tuning effort in the coming year.

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

†URL: `http://charm.cs.uiuc.edu/`

BTA UNIT: S

TITLE: Computational Facility

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% BTA $: 10%

ABSTRACT: Over the last year the Resource has spent signficant energy on upgrading our computational facility's* capacity to analyze the data from our ever-growing simulations, building the infrastructure for our 112 total users (65 remote) to work through the end of our grant period. This work has focused on four major areas: replacing our visitor and researcher desktop systems with full workstations, the upgrade of our primary visualization facility, the continued growth of our disk infrastructure, and a significant increase in our site's security. These upgrades will serve to help all users, particularly the regular visitors to the Resource.

The biggest upgrade in our environment this year has been to the visitor and researcher workstations. Our researchers can now enjoy a Sun W2100z workstation on their desk; these dual-processor Opteron systems offer impressive graphics (nVidia GeForce 6800GT video boards), 4 GB of memory, a DVD burner at the desktop, impressive stability, and twice the processor speed of the previous desktops. We have also upgraded all of our 19" LCD monitors to 21", offering the best resolution the video cards will offer. These systems have offered our researchers the best possible working environment, letting them continue to visualize any but the largest and most complex simulations.

To handle systems that even their desktops cannot handle, we have upgraded our main visualization facility dramatically. Images are now visualized with a Mirage 2000 DLP. This new projector is over ten times as bright as the old system, enough to still be usable with all of the room lights on; its image quality is sharp enough to easily read text, unlike the aging system it replaced. The projector is fully capable of stereoscopic imaging, letting visitors and staff view molecular systems in 3D. To

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

power this projector we continue to use our Sun Fire V880z server, with 32 gigabytes of memory and dual XVR-4000 graphics board. This system is also hooked to the building 3D visualization facility, which is roughly identical to our old system but with more space for guests (40+ people, instead of 10-15).

We are in the process of completing a major upgrade of our computational infrastructure that will better serve our visitors. As of March 2005, we have ordered an additional seven terabytes of disk space, nearly doubling our existing available disk space to a total of 17 TB. These disks are shared to all Resource machines using a total of seven Sun servers, chosen for maximum reliability. 7.5 TB of this space will be backed up nightly using a combination of SuperDLT and LTO-3 tape drives and in-house software.

Finally, in response to security breaches on the National Supercomputer Centers and our own systems, we have implemented much more stringent security policies on our systems without compromising our system's efficiency and wide availability. The most visible addition has been the RSA SecurID authentication system; every user now carries a small keyfob with an ever-changing password, which is necessary to connect to our site remotely. This system ensures that stolen passwords will no longer be a remote security risk. Additionally, we have locked down our network infrastructure in a manner similar to a firewall; only that network traffic which is specifically authorized, such as web and email traffic, is allowed through to our network. Finally, we have reinstalled all of our 250+ systems, simplifying our network layout while keeping security a top priority every step of the way. Overall, our network should now be much more reliable and resistant to an attack as a result of all of these changes.

The total number of raw Service Units awarded to us by the National Resource Allocation Center[†] increased from last year by about 700,000 SUs, primarily on the National Teragrid. This has translated to a nearly 40% increase in scaled compute power. This time is supplemented by our local compute clusters, which remain unchanged from last year.

[†]URL: `http://www.ks.uiuc.edu/Development/Computers/nrac.html`

BTA UNIT: D

TITLE: Training

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% BTA $: 10 %

ABSTRACT: Modeling the molecular processes of biological cells is a craft and an art. Techniques like theoretical and computational skills can be learned by training, but meaningful applications are achieved only with experience and sensitivity. The Rhands-on R workshops in computational biology attempted to teach both the craft and art of modeling through learning-by-doing: participants from all over the world came to the workshop sites to stretch proteins, pull water through molecular channels, mine genomic data, and study their favorite biomolecules. After lectures and discussions in the morning, afternoon sessions were devoted to learning by doing, assisted by 300 pages of tutorials, and supported by 20 laptops purchased and formatted by the Resource for the workshops, each humming with computational biology software, such as VMD, NAMD, and Spartan.

Lectures in the workshops included topics ranging from statistical mechanics of proteins to modeling large systems. Talks started with introductory molecular biophysics material, then advanced to more in-depth material involving molecular dynamics, numerical methods, and large system modeling. The hands-on laboratory tutorials in the afternoons gave students the chance to use the information learned in the morning lectures. The tutorials were written for the workshops, or were previously written tutorials that received careful revision since a prior summer school and through their use in graduate-level courses. The participants were trained in using molecular modeling and analysis software, then later were able to use that knowledge to perform simulations on their own. Most participants were experimental researchers.

Full and detailed evaluations were taken after each workshop. Students answered survey form questions about the teaching methods, techniques, and material in general, as well as about individual lectures and tutorials.Results were positive; nearly all participants stated they gained much from the school.The knowledge that participants took with them from the workshops will be passed on to others. The workshops, funded by NCSA and NIH, may have lasted only a short time, but will go on much longer: all workshop materials remain available on the Resource website*, and the Resource is organizing presently three future workshops: Lake Tahoe (May 23-27), Chicago (June 9-13), and San Francisco (June 26-30).

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

The NCRR Resource for Macromolecular Modelling and Bioinformatics supports NIH researchers and others in the investigation of the physical mechanism underlying cellular processes, providing computational technologies that combine structural and sequence data with mathematical and computational modeling. Sample investigations focus on membrane energy transduction and transport as well as on cell mechanical functions. Technologies include molecular graphics and sequence analysis (VMD), molecular dynamics (NAMD), and grid computing (BioCoRE). The computer programs VMD, NAMD, and BioCoRE are continuously enhanced and distributed freely. Researchers receive training and opportunities for on-site collaboration. Both bench scientists and advanced modelers are served. Software and training material of the Resource are distributed free of charge through a much visited web site.

Three core activities focus on technological development:

1. The program VMD for displaying static and dynamic structures, for sequence information, for structure generation and dynamic analysis is continuously enhanced and adapted to the needs of NIH researchers. Presently, the program's sequence alignment and multiple viewing features are being extended along with features made possible through last generation graphics boards. VMD had become in the previous years extremely popular and due to the inclusion of sequence analysis into the future releases as well as the inclusion of multiple views. The successful development reflects to a large degree the effort by Professor Zan Luthey-Schulten and coworkers. On the graphics and structure / dynamics side, VMD has seen major improvements based on a far reaching reprogramming of the graphics algorithms used. This has lead to a new cartoon representation that will find its way into numerous publications by VMD users. Computer graphics technology has enjoyed and is still enjoying dramatic advances. VMD is uniquely prepared to take advantage of these advances, for example, through programmable shading or through serving 64 bit processors that permit analysis of many gigabytes of structural data as needed for trajectory analysis. The most dramatic development is that VMD is capabable of loading the entire protein data bank (over 30 Gigabytes) in one session with yet unimaginable opportunities for structure comparision that we begin to exploit presently.

2. The molecular modeling program NAMD for a wide user group and many platforms as well as for large scale modeling of cellular systems and massively parallel computers continues to be adapted to serve experimentalists as well as advanced modelers in taking advantage of computer cluster and new processor technologies to accelerate both small scale and large scale modeling. NAMD provides an "imaging tool" for biomolecular systems that is accessible to novice users such as experimentalists, triggers insights through hands-on interaction with the simulation, provides fast results by scaling to the fastest supercomputers available, and is readily adaptable to the unique requirements of novel simulations such as those employing a mix of all-atom and coarse-graining techniques.

3. The program BioCoRE for grid computing and research management along with program modules that integrate with VMD as well as NAMD for all key research needs in cell biology modeling are are being developed further. The goal is to enhance the productivity of NIH researchers in completing entire modeling projects through the provision of complete program libraries that generate and exchange needed data in a seamless fashion. For the proliferation of BioCoRE the Resource will develop tutorials describing how the software can be used to organize researchers' groups, teaching, collaborations, and computing. We will integrate BioCoRE with VMD and develop "open" BioCoRE projects that utilizes BioCoRE for web sites and open access data bases. VMD, NAMD, and BioCORE with yet to be developed modeling modules will provide a comprehensive environment for physical modeling of biological cells. We seek to collaborate with the Stanford National Center for Biomedical Computing to develop such environment that works in a seamless way with software developed at Stanford. The major new concept is project-oriented software that enhances user productivity. By providing a consistent user experience, researchers will be able to perform novel simulations with less preparation time and a shorter learning curve.

The Resource engages also in the generic activities of Collaborations, Sevice, Training and Dissemination:

4. Collaborations apply the Resource's most advanced modeling capabilities to highly relevant cellular systems investigated by leading intramural and extramural experimentalists making its computational infrastructure and expertise in the field of molecular simulations available. The Resource has completed 24 joint publications through these collaborations last year and completed seven collaborative projects Currently, the Resource is engaged in 22 different collaborations. Over the next year, the Resource will continue to closely work with research groups that need to complement their ongoing research with simulation methodologies or plan to integrate computational methods in their research. Planned collaborations include the simulation of ribosome, bacterial flagellum, and the whole virus, clearly reflecting the unique strength of the Resource in large scale simulations of biomolecular systems.

5. Service is provided for the Resource software VMD, NAMD, BioCoRE through responses to user inquiries, support of user groups, maintenance of program libraries, provision of a visitor and training center as well as an advanced computer laboratory. We will continue to offer technical advice, e.g., on building computer clusters and visualization facilities, to both external users and users of our major software packages, and we will maintain our excellent seminar series. Furthermore, we plan to improve our visitor program into a full-fledged visitor center, increasing the quantity of researchers utilizing our technical facilities, and improving the quality of the environment that they work with.

6. Training will continue to be available through a new electronic text book as well

as through an ongoing series of workshops based on introductory lectures along with a system of tutorials and data files for self-study on key platforms (Windows, Linux, Mac). Our training efforts have been focused greatly on hands-on workshops that have reached already about three hundred participants. The Resource has written tutorials for self-study, and has 20 Macintosh laptops for workshop participants to use, each acting as a complete package with all the necessary tutorial files and software. We plan to expand our teaching and training in several ways including writing an electronic and printed textbook and re-writing the tutorials to extend them to platforms other than the Macintosh laptops. As most of our current training methods are geared toward graduate students, we will also explore new options for undergraduate training.

7. Dissemination is achieved through a widely used web site for downloading of software and training material and for showcasing exemplary modeling projects as well as through scientific publications and lectures. Over the past year, dissemination took place in the traditional formats including 34 publications in refereed journals, 60 talks, outreach activities such as special lectures series, responding to image requests, and licensing. The Resource has also been covered by various external media agencies. However, the tool with the widest outreach to the scientific community is the Resource website, with approximately 423,000 visitors, 985 gigabytes of downloads, and nearly 1,000 links to the home page over the past year. Maintaining this level of website success requires that the Resource engage in an ongoing process of revision, update, and exploration of what the website can provide to the biomedical community. Planned improvements include addition of various features to the software application websites, and revised, reorganized and updated research and training pages. Furthermore, new pages will be created, devoted to description of prior and current collaborations, and to summarizing news from and about the Resource. The Resource is also working with professional website designers to develop a new 'look' for the Resource website.

Highlights

Molecular Basis of Hearing

The ear is a robust and sensitive device, able to perceive the faint sound of a coin hitting the floor to the thunderous sound of a plane engine. Not only can the ear deal with stimuli of such different intensity, but it is also able to exquisitely distinguish a wide range of sound frequencies. The ear transforms a complex, mechanical stimulus (sound), into an electrical signal understood by the brain. This process is called mechanotransduction, and over the last two decades biophysical studies have characterized the structures involved in this task, the hair cell's bundle of the inner ear.

Stereocilia in each hair cell bundle are arranged in rows of increasing height, and a fine filament, termed the "tip link", connects the tip of each stereocilium to the side of its taller neighbor. Tip links are thought to connect directly to transduction channels, so that deflections of a hair bundle caused by sound —that would tighten tip links— open these ion channels, and thus induce an electrical signal (Fig. 1).

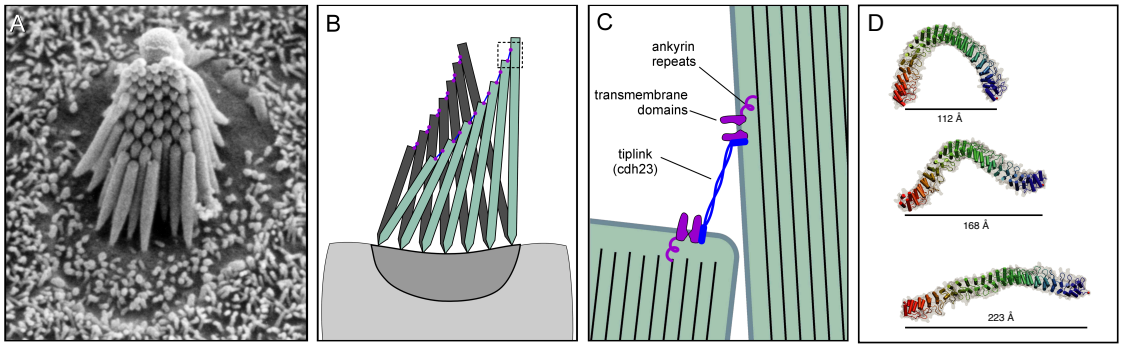

Figure 1: Mechanotransduction in hair cells of the inner ear. (**A**) Scanning electron micrograph of a hair bundle (bullfrog sacculus, Corey's lab). This top view shows the stereocilia arranged in order of increasing height. (**B**) Model for mechanotransduction. Deflection of a hair cell's bundle induced by sound causes the stereocilia to bend and the tip links between them to tighten. (**C**) Ion channels attached to intracellular elastic elements (ankyrin repeats) open in response to tension conveyed by inextensible tip links, as suggested by experiments and our simulations [9]. (**D**) Elastic response of ankyrin repeats. Our simulations have shown how the structure elongates through changes in curvature without modifying its secondary structure [9].

In recent years, proteins making up the transduction apparatus have begun to be identified. The tip link is composed in large part of cadherin 23 [1–3], whereas the transduction channel is likely formed by subunits of the TRP channel family containing multiple ankyrin repeats in their cytoplasmic termini [4–8]. The challenge at this point is to correlate the experimentally determined properties of the transduction apparatus with the proteins it comprises. Moreover, the identification of the functional role of each protein is required to understand hereditary diseases causing deafness (e.g., Usher syndromes).

In order to confront this challenge, the Resource has used the computer as a virtual

microscope*. An important step in characterizing the elastic behavior of cadherin and ankyrin has already been accomplished and reported in a joint publication with our collaborator, David P. Corey [9]. Following earlier work [10], the elastic properties of cadherin were determined and forces needed to stretch this protein were found to be too large to explain mechanotransduction in hearing. However, simulations revealed that ankyrin can be stretched by weak forces that change the protein's overall shape (tertiary structure elasticity) while leaving the secondary structure intact (Fig. 1 D). The elastic properties matched those of the "gating spring" in hair cells postulated earlier on the basis of observations [3,11–13]. The simulations carried out by the Resource also revealed that ankyrin protects the transduction apparatus against extreme stimuli by unfolding sequentially its secondary structure upon application of strong forces. Future studies will focus on the temperature and salt concentration dependence of ankyrin elasticity, as well as on how particular mutations related to hereditary diseases affect ankyrin and cadherin causing deafness.

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

Nanopore Device for High-Throughput DNA Sequencing

A human genome contains about 3 billion base-pairs, which sequence comprises the genetic blueprint of the entire organism. Certain variations in the genome sequence, either inherited at birth or acquired with time through mutations, are known to cause serious health problems; early detection of the genome abnormalities increases the chances for a successful treatment. With current technology, individual genomes can be determined to the desired 99.99 % accuracy within about two months for approximately 10 millions of dollars, which is still too lengthy and too costly to be prevalent in personal medicine. As research in nanotechnology extents the tools for fabrication of integrated circuits to nanometer dimensions, alternative technologies for faster and cheaper DNA sequencing may emerge. We suggest a device for high-throughput DNA sequencing to be built around a 2-nm-diameter pore in a thin (2-5nm) silicon membrane [58]. The sequence of a DNA molecule can be discerned by such a device in principle through a semiconductor detector, integrated with the pore, that record electrical signals induced by the DNA molecule passing through the pore. In an ongoing collaboration with UIUC electrical engineers developing such nanopore sensors, the Resource has been conducting molecular dynamics simulations of DNA translocation through synthetic nanopores and computing the electrical signals produced by the DNA translocation *.

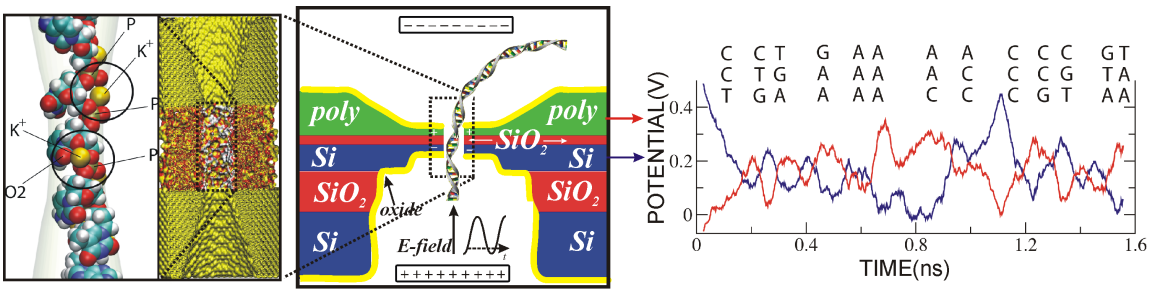

Figure 2: Detecting DNA sequence with a nanopore sensor. (*Center*) The scheme of the nanopore sensor (G. Timp), that is built around a nanopore in a multi-layer synthetic membrane. (*Left*) Microscopic models of a DNA strand confined inside a 1.0-nm-diameter pore, and of a nanopore in a multi-layer synthetic membrane. (*Right*) Electrical signals produced by the DNA strand translocating through a nanopore, as predicted my MD simulations. The recording suggests that individual nucleotides can be resolved (counted) with a nanopore sensor.

In order to relate the sequence of DNA to the measured electrical signals it is essential to characterize DNA conformations inside the pore in atomic detail. Molecular dynamics simulations are used in this project as a kind of a computational microscope to provide dynamic images of the nano-device. A typical system simulated and imaged by us includes a patch of a silicon membrane dividing electrolyte solution into two compartments connected by the nanopore. A DNA molecule is placed in front of the pore. External

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

electrical fields capture the DNA molecule from the solution and subsequently translocate it through the pore. Measuring duration of DNA translocation at experimental fields brought about estimates of the resolution that the bio-electrical sensor should have in order to detect DNA sequences. Visualizing interaction of DNA with the surface of the pore revealed hydrophobic adhesion of DNA bases to the pore walls that may slow down or halt DNA translocation. Varying geometry of the pore in MD simulations allows screening of possible DNA conformations and identifying those that produce strongest sequence-specific electrical signals. Future work will address design of ideal nanopore shapes, coatings of nanopore walls, application of mechanical forces on one or both sides of the nanopore to translocate DNA in a more controlled way, as well as the application of various types of electrical field, e.g., alternating fields. The future simulations will also study the signatures in various electrical recordings that can be obtained in principle, along with the error bars expected.

This work has recently been reported in two publications [55, 56], two more have been submitted [57, 58].

Imaging the Permeability of a Membrane Channel with Molecular Dymanics.

In a living organism, membrane channels act like miniature valves regulating flow of ions and other solutes between intracellular compartments and across the cell's boundaries. Assembled in complex circuits, membrane channels generate, transmit and amplify signals orchestrating healthy function of the entire organism. As more membrane channels become structurally known, understanding their regulatory function requires a methodology that can relate the atomic-resolution structures to channels' permeability for different solutes.

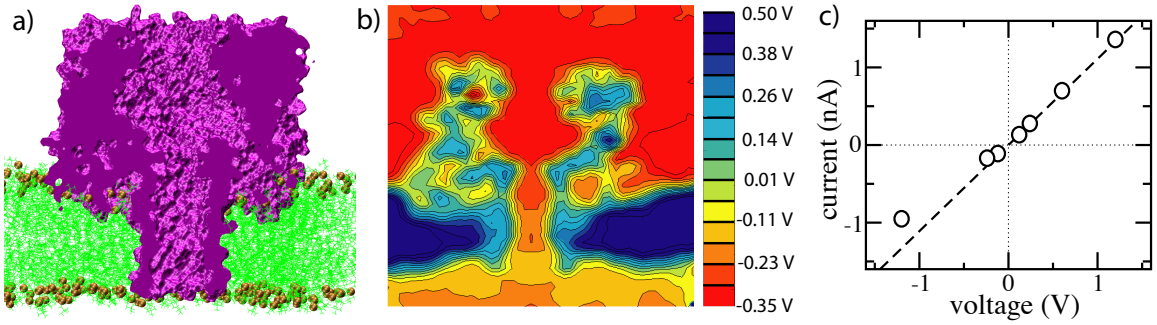

Figure 3: Computing the current/voltage dependence of a membrane channel with all-atom molecular dynamics. (**a**) A microscopic model of a membrane channel is constructed. (**b**) In a MD simulation, a transmembrane potential is generated by applying an external electric field. (**c**) The current is computed by tracing local displacements of the ions. Repeating simulation at different applied fields yields the current/voltage dependence.

Until recently, theoretical investigations of ion permeation were limited to reduced models, in which a membrane channel, a cell membrane, and water were approximated by slabs of uniform dialectric. Ionic currents were generated by a continuum electrostatic potential driving an ensemble of charged particles through a rigid pore shaped like a transmembrane channel. Dramatic increase in computational power and its efficient utilization by the highly parallel molecular dynamics code NAMD made the first calculation of ionic currents within an all-atom model possible. In a recent study [90], the Resource has demonstrated that ionic conductance of the α-hemolysin channel can be accurately predicted at experimental conditions from MD simulations, revealing the molecular mechanism of the pH gating in α-hemolysin *.

This study inaugates a new computional technology for investigating the permeability of membrane channels. For the first time the current/voltage property of a membrane channel can be computed from the first principles, as illustrated in Fig. 3. The method's accuracy depends on how many ion permeations can be observed within the simulated

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

period of time. From a 100 ns simulation one can expect to resolve currents of 1pA. Thus, within the next few years, the accuracy of numerical experiments will become comparable to that of a patch-clamp, which promises an extensive deployment of the computational technology for measuring ionic currents throughout the biophysical community.

Grant Number: P41RR05969
Report PD: (8/1/04 – 7/31/05)

VMD: Visualization and Analysis of Biomolecular Information

The growth of bioinformatics data in recent years has changed the face of biomolecular modeling. Structures must be examined in the context of their conserved sequences, relation to functionally similar proteins, and their role in the genome. The Resource has integrated a multiple structure alignment plugin into VMD*, our molecular visualization and analysis plugin. Using the multiple alignment plugin a researcher can load a set of biologically related structures, perform structure and sequence aligments, construct a phylogenetic tree which describes the evolutionary relationship between the loaded structures, view the set of aligned structures superimposed on each other while interactively highlighting conserved residues. Using the multiple alignment plugin, researchers can identify residues likely to be involved in protein function by analogy with conserved residues in well-studied proteins. Although tools for performing various types of sequence and structure alignment have been available for some time, the inclusion of the multiple alignment plugin in VMD 1.8.3 puts this capability in the hands of thousands of researchers in a convenient and easy-to-use form, taking advantage of the unique visualization features provided by VMD. The multiple alignment plugin is one of several major features added to VMD during the funding period.

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

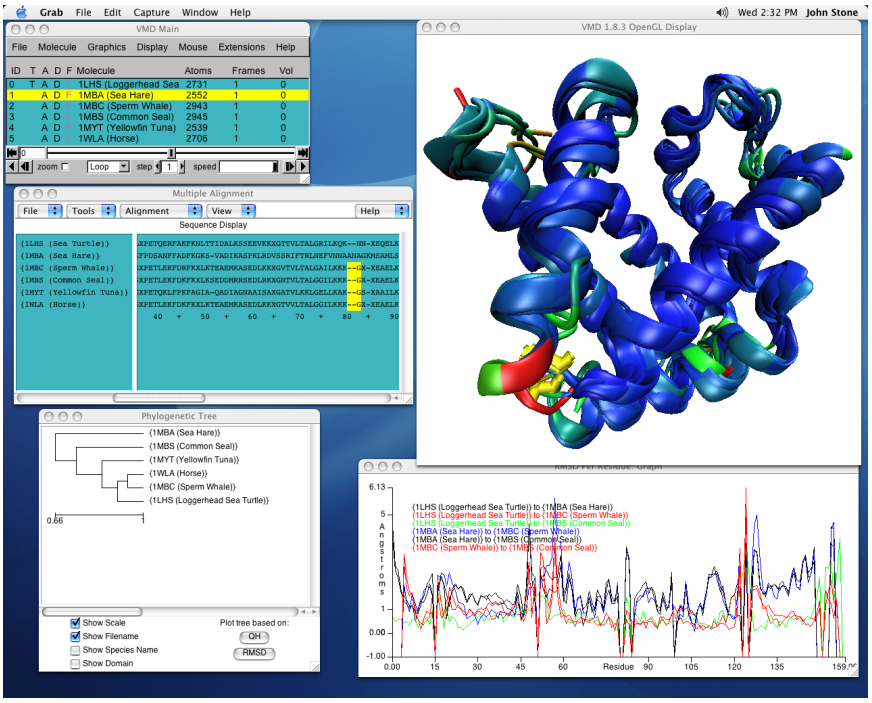

Figure 4: VMD 1.8.3 running on MacOS X. A set of myoglobin structures from different species are shown structurally aligned and superimposed in 3-D, a phylogenetic tree illustrates the evolutionary relationship between the loaded structures, and the per-residue RMSD values are plotted indicating structural conservation. Newly-developed 3-D secondary structure representations show protein structure in a simplified graphical form while retaining the key elements of shape in a manner faithful to full-detail graphical representations. The use of cutting-edge graphics technology such as OpenGL Programmable Shading Language allows researchers to interactively display biomolecules with visual fidelity previously achievable only with batch mode rendering software.

Another key area of development in the past funding period has been targeted on advancing the use of computer graphics technologies to address the visualization needs of cutting-edge molecular dynamics simulations. Newly designed graphical representations released in VMD 1.8.3 allow researchers to view secondary structure representations of proteins with better geometric accuracy and visual quality. This improved secondary structure representation helps researchers immediately recognize key architectural features of protein structures, particularly when comparing groups of biologically related structures. Other developments include new features for creating figures of proteins containing pores and voids with sets of slicing planes and fast interactive display of isosurfaces. The electrostatic potential of a protein plays a role in protein folding and stability, and is strongly affected by the geometric shape of its surface. Several new tools within VMD provide the means to calculate and display display isovalue surfaces of electrostatic fields, color protein structures by electrostatic potential, and directly view long-range electrostatic potentials in molecular dynamics simulation [90].

Workshops in Computational Biology

Figure 5: TCBG Workshops

The Resource conducted three workshops, one in Perth, Australia from June 7-18, 2004*, a second in Urbana, Illinois from November 8-12, 2004†, and a third in Boston, Massachussetts from December 5-9, 2004‡. The workshops were designed to introduce a wide range of physical modeling and computational approaches used for the simulation of biological systems and the investigation of their function at an atomic level. The workshops were designed for graduate students and postdoctoral researchers in biophysical fields to extend their research skills to include computational and theoretical expertise, as well as other researchers interested in theoretical and computational biophysics.

Modeling the molecular processes of biological cells is a craft and an art. Techniques like theoretical and computational skills can be learned by training, but meaningful applications are achieved only with experience and sensitivity. The 'hands-on' workshops in computational biology attempted to teach both the craft and art of modeling through learning-by-doing: participants from all over the world came to the workshop sites to stretch proteins, pull water through molecular channels, mine genomic data, and study their favorite biomolecules. After lectures and discussions in the morning, afternoon sessions were devoted to learning by doing, assisted by 300 pages of tutorials, and supported

*URL:`http://www.ks.uiuc.edu/Training/SumSchool/2004/`

†URL:`http://www.ks.uiuc.edu/Training/Workshop/Urbana/`

‡URL:`http://www.ks.uiuc.edu/Training/Workshop/Boston/`

by 20 laptops purchased and formatted by the Resource for the workshops, each humming with computational biology software, such as VMD, NAMD, and Spartan.

Lectures in the workshops included topics ranging from statistical mechanics of proteins to modeling large systems. Talks started with introductory molecular biophysics material, then advanced to more in-depth material involving molecular dynamics, numerical methods, and large system modeling. The hands-on laboratory tutorials in the afternoons gave students the chance to use the information learned in the morning lectures. The tutorials were written for the workshops, or were previously written tutorials that received careful revision since a prior summer school and through their use in graduate-level courses. The participants were trained in using molecular modeling and analysis software, then later were able to use that knowledge to perform simulations on their own. Most participants were experimental researchers.

Full and detailed evaluations were taken after each workshop. Students answered survey form questions about the teaching methods, techniques, and material in general[§], as well as about individual lectures and tutorials[¶]. Results were positive; nearly all participants stated they gained much from the school.

The knowledge that participants took with them from the workshops will be passed on to others. The workshops, funded by NCSA and NIH, may have lasted only a short time, but will go on much longer: all workshop materials remain available on the Resource website, and the Resource is organizing presently three future workshops: Lake Tahoe (May 23-27), Chicago (June 9-13), and San Francisco (June 26-30).

[§]URL:`http://www.ks.uiuc.edu/Training/Workshop/Boston/evaluationform.pdf`

[¶]URL:`http://www.ks.uiuc.edu/Training/Workshop/Boston/BostonWorkshop-LTFeedback.pdf`

Organization

Organizational Structure The Resource web site is a center point of our organization, used internally for administrative, scientific, and computing needs, and externally as a key access point for the biomedical community to review our collaborative work and developmental efforts and to take advantage of our service, training, and dissemination activities. Virtually all of the Resource's operational data (research, development, management, and system administration) are stored and distributed internally through locally developed web-based databases. Similarly, the publicly accessible external website represents our extensive effort to communicate our science to the biomedical community, through journal articles and other papers, various media (images, movies, streaming video) capturing our science, summaries of Resource research areas, access to all Resource-produced software, a list of our services, educational, and other content reflecting the work of the group.

The Resource's web site represents our way of seeing and doing things both within and beyond the Resource's formal boundaries, and also represents what we view as the mission of the Resource. Recent additions to our external website include extensive documentation of our workshops, including all lectures slides, links to tutorials, participant descriptions, and evaluation results. Training pages have also been developed that provide links to constantly updated tutorials used in the workshops.

K. Schulten (Professor, Physics, Beckman, Biophysics, Chemistry) is the Principal Investigator and Program Director of the Resource. E. Tajkhorshid, the Assistant Director for Research of the Resource, assists the Director in all organizational and scientific activities of the Resource. L. Kale (Professor, Computer Science) and Z. Luthey-Schulten (Professor, Chemistry) are other Co-Principal Investigators of the Resource. D. Brandon is the Manager of the Resource who coordinates all organizationl and Dissemination activities. Tim Skirvin is the Systems Administrator of the group who also oversees Service activities of the Resource. The Resource is located at the Beckman Institute for Advanced Science and Technology and K. Schulten, the Resource Director, administratively reports to the Institute Director. The Institute Director reports to the University of Illinois Vice Chancellor for Research.

The Resource members come from a spectrum of disciplines, each of which contributes significantly to the intricate fabric of the Resource's goals and activities. Staff and graduate students are affiliated with fields and departments such as Physics, Computer Science, Biophysics, Chemistry, Mathematics, and Electrical and Computer Engineering.

All Resource members participate in the daily operation of the facility. Members attend weekly group and subgroup meetings, are responsible for specific maintenance tasks at the Resource, attend and present talks in group seminars, and keep continuously informed by spending time at the Beckman Institute as well as through email, various BioCoRE

project groups, and the Resource's internal web site which lists meetings, seminars, group jobs, and more.

The PIs and affiliated faculty, in consultation with the other Resource members, determine collaborative and service projects. Selection of technological research and development projects at the Resource is determined by the following criteria:

- Relevance of research to the biological and medical sciences
- Quality and originality of research and conceptual approach
- Computational demands of the research project
- Novelty of algorithmic strategies required for the projects

Continuous interactions with the collaborators and ongoing critical evaluation of the projects ensure relevance, progress and adherence to the criteria outlined above. Local and remote computer time is allocated to projects as needed.

The web-based Resource manual, as well as other useful documents available on our internal site serve as guidelines for new members and as reference resources for old members.

The continually evolving internal site reflects short-and long-term objectives and describes the Resource's structure and daily procedures; it specifies policies and guidelines; it contains a job list detailing the maintenance tasks assigned to Resource members; it offers detailed information on reports, proposals, and special events. The internal site has a vital role in streamlining and systematizing the Resource operation via tips and information on the Resource's internal processes, and on Beckman and UIUC facilities and procedures.

How to Acknowledge Resource Support A prominent link on the front page of the Resource's external site, as well as links at each application website, leads users and beneficiaries to guidelines on how to acknowledge Resource support in several ways, depending on resources used.

Service, Training and Dissemination

Introduction to Service, Training and Dissemination

Our service, training, and dissemination efforts are boundary-spanning activities through which we transfer the outcomes of our work and deliver technologies and knowledge to the biomedical community. These core activities can be classified into two general, sometimes overlapping, functional areas:

I. Technological development to create research tools and methods

II. Research and collaborative projects that use and benefit from the tools

Both of these activity areas have vast potential and practical implications for the Resource and the biomedical community at large. The outcomes of our technological developments and the results of our collaborative efforts are transferred to the biomedical community via our broad and numerous service, training, and dissemination activities.

Forces such as the huge genomic data revolution and the increasing pace of structure discovery, the explosive progress in hardware development and web technology, along with other factors have infused renewed energy and urgency to our activities and are reshaping our scope and practices daily. The growth of the Resource continues, with 46 members (graduate assistants, postdoctoral associates, developers, faculty, administrative and technical staff); the number and size of systems modeled here are unmatched; and, our computational resources are much bigger than ever before and are effectively utilized.

Thanks to the web, the Resource's visibility has expanded greatly, and with that, the service, training and dissemination opportunities, and the complexity of our relationship with our environment have widened tremendously.

In the past year we have continued to rely on web technologies as our key service, training and dissemination vehicles. Our emphasis on web technologies allows us the flexibility to make our technological developments and collaborative efforts accessible across increasingly blurry organizational boundaries. Immense opportunities for better administration, service, training and dissemination are available now, but with them come related issues such as intellectual property, ownership, copyright matters, licensing, and more that have to be considered and addressed.

Our efforts over the past year have been to work to make training as prominent on our website as our service and dissemination activities. The Resource also devoted substantial resources to conducting three workshops in computational biophysics, and developing tutorials for those workshops, with all resulting materials placed on the website.

Service

The Resource offers the biomedical community a variety of services as outlined below. Most of the services are well documented on our web site and, whenever possible, are completely web-based for easy access and use. The Resource is known, in particular, for its effective support of scientific collaborations, as evidenced by the collaborative projects outlined earlier in this report.

Computational Resources. In the past year the Resource's computational facilities have benefited members, their collaborators, and others engaged in research projects related to Resource expertise and areas of study.

112 researchers have used the Resource's computational facilities (47 local, 65 remote). By June 2005, the Resource will have experienced an increase of over 140% in shared file storage space compared to the same period a year ago (from 7.0 to 17.0 TB). Local compute power and visualization capabilities remains strong, and external supercomputer time has again been allocated, raising the Resource's scaled compute power by 40%.

Our knowledge of visualization solutions, large-memory computers, web utilization, and computational clusters has been of specific use to the biomedical community and to the scientific community in general; many researchers and organizations have requested and received our technical advice for the development of their local facilities. These include (in chronological order starting in early April 2004):

- Beckman ITG (shell scripting and SSH help)
- Northwestern University (cluster building)
- University of Mississippi (SecurID system and SSH)
- The University of Texas MD Anderson Cancer Center (disk space)
- Southern Illinois University - Edwardsville (biophysics library)
- Tulane University (cluster building)
- Northwestern University (network advice)
- University of Illinois at Urbana-Champaign, Computational Electronics Group (queuing systems)
- Math.Net (Apache system configuration)
- University of Illinois at Urbana-Champaign, School of Chemical Sciences (LCD projector)

- University of Illinois at Urbana-Champaign, School of Chemical Sciences (cluster building)
- Duke University (cluster building)
- International Paper Company, Memphis, TN (DVD burner compatibility)

The Resources technology area has kept abreast of the latest developments in the market, in particular, by maintaining relationships with leading hardware vendors and testing our software on their products. For example, in the past year the Resource tested next-generation OpenGL drivers for the 3DLabs Wildcats Realizm 100 graphics card before their public release, and expects to test a new Sun video board in the near future. Among other benefits to our users, such cutting edge testing increases the likelihood of easily porting our software once the hardware is available on the market.

Resource Collaborations. Through collaborations between members and experimentalists, the Resource provides services to groups and individuals who lack the computational resources and skills themselves. Information on the content and scope of the Resource collaborative projects is available earlier in this report. The collaborations anchor the Resource in highly relevant applications and ensure that our researchers are aware of real-world challenges.

Resource Software. The Resource is engaged in intensive developmentefforts and technology transfer. We distribute a number of software packages, particularly VMD, NAMD and BioCoRE, as well as a number of smallerprograms. All Resource-developed programs, binaries and source, are freely available on our web site for easy accessibility, employing where needed a unified distribution mechanism.* In this report we are focusing on the distribution and support accomplishments of VMD, NAMD and BioCoRE, in the past year.

Use of VMD, NAMD, and BioCoRE. 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.

VMD has 55,422 registered users (an increase of 13,059 in the least year), with 12,272 of those users repeat users (i.e., they have downloaded more than one version of VMD), and 19% of all registrants having NIH funding. There are 19,000 users of VMD 1.8.2, with 10,000 new users in the last year. Within four months of its February 2005 release, VMD 1.8.3 had acquired 6,300 users.

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

NAMD has 12,095 registered users (an increase of 2,813 in the last year), of whom 2,122 are repeat users. 1,940 (16%) of NAMD users are NIH funded. The latest version, NAMD 2.5, has 5,862 users, of whom 1,011 are NIH funded. NAMD has been downloaded 12,035 times in the past year.

BioCoRE has 1,059 registered users (an increase of 208, or an increase of +24% in the past year), involved in 322 projects (compared to 228 a year ago). And, 127 projects within BioCoRE have been reported as either fully or partially NIH-funded.

The software release schedule of the Resource's lead programs reflects great productivity and lively activity:

- VMD: 1.8.3 released February 2005
- NAMD: 2.6 expected June 2005
- BioCoRE: Incremental updates every few weeks;[†] next generation environment and polls/quizes module released December 2004

Software Licensing. The Resource maintains ongoing discussions with the UIUC Office of Technology Managment, industry, and others to develop licenses that allow broad distribution of our software. In the last year, the Resource provided 24 software disclosures from the MDTools compilation to the UIUC Office of Technology Management, with an emphasis that the university place all of these tools under an open-source license. Further, the Resource in cooperation with the UIUC Office of Technology management negotiated a license with Scienomics[‡], a company based in Paris, France to distribute NAMD as part of their central software package.

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 the software sections on our web site had been visited as follows:

Development, Distribution, and Use of VMD

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.

[†]URL:`http://www.ks.uiuc.edu/Research/biocore/announce/changeLog.shtml`

[‡]URL:`http://www.scienomics.com/`

	Total	Month Avg.
VMD	149,082	16,233
NAMD	60,722	7,013
BioCoRE	18,673	2,140

Table 1: Application web site visits

VMD Enhancements for 2004-2005 include:

- New multiple structure and multiple sequence alignment plugin
- New secondary structure representation which faithfully represents biomolecular structures with unusually curved helices
- Support for OpenGL Shading Language and programmable shading for high quality interactive rendering of molecular graphics using inexpensive video game-oriented graphics accelerators
- Support for computers containing 64-bit processors from AMD and Intel, allowing researchers to efficiently view and analyze million atom biomolecular simulations
- Ability to color molecular structures by electrostatic potential, probability density values, and other volumetric data
- Plugin for easy calculation and visualization of PME electrostatic fields
- Built-in commands for calculating solvent-accessilble surface area
- Support for more than 20 new molecular data file formats
- Easy-to-use graphical user interfaces for several existing plugins

VMD Posters/Presentations/Demos/Tutorials/Talks (local and remote, by Resource members and others who informed us):

- June 7-18, 2004, Perth, Australia, *Workshop in Computational Biology.* Tutorial: "VMD Tutorial" (Resource staff)
- November 8-11, 2004, Pittsburgh, PA, *IEEE/ACM SC2004 Conference.* Presentation: "Exploring Biomolecular Machines with Supercomputers" (James Phillips)
- November 8-12, 2004, Urbana, IL, *Workshop in Computational Biology.* Tutorial: "VMD Tutorial" (Resource staff)

- December 5-9, 2004, Boston, MA, *Workshop in Computational Biology.* Tutorial: "VMD Tutorial" (Resource staff)
- December 8-9, 2004, Nance, France, *INRIA/CNRS ARC Docking Project.* Presentation: "VMD Biomolecular Visualization and Analysis" (John Stone)
- February 15, 2005, Urbana, IL, *Beckman Institute - Imaging Technology Group Forum.* Lecture: "Dancing Proteins: 3-D Visualization of Protein Structure and Dynamics on Next-Generation Graphics Hardware" (John Stone)
- February 22, 2005, University of Missouri at Rolla, Rolla, MO, Department of Computer Science *CS Colloquium.* Lecture: "Dancing Proteins: 3-D Visualization of Protein Structure and Dynamics on Next-Generation Graphics Hardware" (John Stone)
- February 25, 2005, Purdue University, West Lafayette, IN, *Envision Center.* Lecture: "Dancing Proteins: 3-D Visualization of Protein Structure and Dynamics on Next-Generation Graphics Hardware" (John Stone)

Scope of VMD User Support:

- 513 subscribers to the VMD-L mailing list, with 4696 total postings, and 1703 postings since the end of April 2004
- Local face-to-face support has been provided

234 individuals outside of the Resource have access to the VMD CVS tree revision control system.

List of papers citing VMD: A literature search in the ISI Web of Science citation database in April 2005 yielded 911 published journal articles, papers, or books citing the VMD origin paper [85], with 324 citations occurring over the past year:

1. V. A. Likic, A. Perry, J. Hulett, M. Derby, A. Traven, R. F. Waller, P. J. Keeling, C. M. Koehler, S. P. Curran, P. R. Gooley, T. Lithgow, "Patterns that define the four domains conserved in known and novel isoforms of the protein import receptor Tom20." *Journal of Molecular Biology*, 347:81-93, 2005.
2. S. Ulmschneider, U. Muller-Vieira, C. D. Klein, I. Antes, T. Lengauer, R. W. Hartmann, "Synthesis and evaluation of (pyrictylmethylene) tetrahydronaphthalenes indanes and structurally modified derivatives: Potent and selective inhibitors of aldosterone synthase." *Journal of Medicinal Chemistry*, 48:1563-1575, 2005.

3. M. K. Petersen, F. Wang, N. P. Blake, H. Metiu, G. A. Voth, "Excess proton solvation and delocalization in a hydrophilic pocket of the proton conducting polymer membrane narion." *Journal of Physical Chemistry B*, 109:3727-3730, 2005.

4. S. Andre, H. Kaltner, M. Lensch, R. Russwurm, H. C. Siebert, C. Fallsehr, E. Tajkhorshid, A. J. R. Heck, M. V. Doeberitz, H. J. Gabius, J. Kopitz, "Determination of structural and functional overlap/divergence of five proto-type galectins by analysis of the growth-regulatory interaction with ganglioside GM(1) in silico and in vitro on human neuroblastoma cells." *International Journal of Cancer*, 114:46-57, 2005.

5. Y. Q. Shen, N. L. Zhukovskaya, Q. Guo, J. Florian, W. J. Tang, "Calcium-independent calmodulin binding and two-metal-ion catalytic mechanism of anthrax edema factor." *Embo Journal*, 24:929-941, 2005.

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Sites with Links to the VMD Site (Google, April 2005): 186 domains; 202 sites; 432 pages.

Development, Distribution, and Use of NAMD

Below we report service rendered by the Resource through its molecular dynamics program NAMD. The program enjoyed during the reported period significant improvements and a further drastic increase in user numbers. The program is widely considered as uniquely satisfying the demand for an effective program on the new generation of teraflop parallel computers.

NAMD Enhancements for 2004-2005 include:

- Port to 512-processor NCSA SGI Altix.
- Port to 640-node UIUC Apple Xserve G5 Myrinet cluster.
- Port to UIUC Parallel Programming Lab Opteron Infiniband cluster.
- Port to and verification of Charm parallel runtime system release 5.9.
- Parallel performance enhancements for IBM Blue Gene.
- Efficient Tcl script interface for adding boundary forces.
- Tcl command to load new charges during simulation.
- Improve load balance for simulations with large fraction of fixed atoms.
- Reduce memory usage for coarse-grained or other sparse simulations.
- PME electrostatics visualization code reimplemented as VMD plugin.

- Requirements analysis and design of NAMD 3 continues.

NAMD Acknowledgements: The Standard Performance Evaluation Corporation, a non-profit corporation formed to develop and endorse a set of guidelines for high-performance computing systems, acknowledged the value of NAMD by electing to use NAMD (via a special agreement) as a parallel processing benchmark for their CPU200x suite of guidelines. This suite measures the performance of high-end computing systems running industrial-style applications and is especially suited for evaluating the performance of parallel and distributed computer architectures. Also in the last year the Resource reached an agreement with Scienomics, a corporation based in France offering tools and service for molecular modeling and simulations, to include NAMD as part of their Materials and Processes Simulations software.

Posters/Presentations/Demos/Tutorials/Talks (local and remote, by Resource members and others who informed us):

- June 7-18, 2004, Perth, Australia, *Workshop in Computational Biology.* Tutorial: "NAMD Tutorial" (Resource staff)
- August 25, 2004, Philadelphia, PA, *American Chemical Society National Meeting.* Demo: "Chemistry by FlashMob 2004" (Michelle Francl-Donnay, Bryn Mawr)
- October 19, 2004, Urbana, IL, *Workshop on Charm++ and Its Applications.* Presentation: "NAMD 3: Designing the Next Generation Scalable Molecular Dynamics Application" (James Phillips)
- November 8-11, 2004, Pittsburgh, PA, *IEEE/ACM SC2004 Conference.* Presentation: "Exploring Biomolecular Machines with Supercomputers" (James Phillips)
- November 8-12, 2004, Urbana, IL, *Workshop in Computational Biology.* Tutorial: "NAMD Tutorial" (Resource staff)
- December 5-9, 2004, Boston, MA, *Workshop in Computational Biology.* Tutorial: "NAMD Tutorial" (Resource staff)

NAMD Availability in Supercomputer Centers:

- Pittsburgh Supercomputing Center
- National Center for Supercomputing Applications
- San Diego Supercomputer Center
- Leibniz Computing Centre at Munich

- Deutsches Krebsforschungszentrum (German Cancer Research Center)

Scope of NAMD User Support:

- The NamdWiki user-editable web site contains 59 customized pages, providing a public whiteboard for sharing NAMD issues and experience; in particular, a general troubleshooting page lists symptoms and solutions for common error messages encountered during runs, and there are pages with advice for building and running NAMD on a specific platform
- 291 subscribers to the NAMD-L mailing list, with 2,019 total postings, and 1,119 postings since the end of April 2004
- Over 800 emails exchanged with users, not counting questions sent to the Charm++ developers or the NAMD and VMD mailing lists (this is a decrease from last year, as users can now find immediate answers by turning to our increasing self-help resources such as the searchable manual and mailing list archives, list of common problems documented on the NamdWiki, and the improved training materials made available from the hands-on workshops)
- Local face-to-face support has been provided

There are currently 172 users with access to the NAMD source code repository, with 55 users added in the last year.

List of papers citing NAMD: A literature search in the ISI Web of Science citation database in April 2005 yielded 193 published journal articles, papers, or books citing the NAMD origin paper [27], with 86 citations occurring over the past year:

1. L. M. Espinoza-Fonseca, J. G. Trujillo-Ferrara, "Structural considerations for the rational design of selective anti-trypanosomal agents: The role of the aromatic clusters at the interface of triosephosphate isomerase dimer." *Biochemical and Biophysical Research Communications*, 328:922-928, 2005.
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Sites with Links to NAMD site (Google, 2005): 86 domains; 88 sites; 203 pages.

Development, Distribution, and Use of BioCoRE

Below we report service rendered by the Resource through its collaboratory tool BioCoRE. The program enjoyed during the reported period significant improvements and starts to become more widely adopted by the community. BioCoRE is ideally suited for making the great investment into the US computational grid eminently useful for biomedical research.

BioCoRE 2004-05 updates include:

- Release of new collaborative environment interface
- Polls and quizzes tool allows soliciting project member feedback
- File management via Webdav made faster, more stable
- E-mail 'watch' tools watches for changes in BioCoRE directories and notifies users

BioCoRE Evaluation

Data collection efforts included the BioCoRE 2005 user survey, in which registered users were asked to complete a web-based survey meant to capture user demographics, the importance of BioCoRE features to users, questions based in usability concepts, perceptions of user support, preferences for future features, overall satisfaction and impact on work, and reactions to open questions.

BioCoRE for Training

BioCoRE continues to be a valuable tool for training support. The collaboratory was used to support a graduate-level course in non-equilibrium statistical mechanics, with students, instructors, and some Resource staff all participating in a BioCoRE project created for the class. BioCoRE's chat tool supported interaction among project members, and the message board served as a posting board for notices about the class. A new feature of

BioCoRE allowed the message board entries to also be e-mailed to students. Homework assignments, class lectures, and tutorials were made available to students via BioCoRE's file system, the BioFS. A parallel project was also created in BioCoRE, and limited to instructional and Resource staff, as a means of coordinating course materials and organization.

BioCoRE Posters/Presentations/Demos/Tutorials/Talks (local and remote, by Resource members and others who informed us):

- October 3-5, 2004, Arlington, VA, *NSF Cyberenabled Chemistry Workshop* Presentation: "BioCoRE" (Kirby Vandivort)
- October 29, 2004, New York, NY, D. E. *Shaw Research and Development Seminar Series* Lecture: "Biomolecular Modeling Today" (Klaus Schulten)

Scope of BioCoRE User Support:

- 194 emails issued to/from `biocore@ks.uiuc.edu` from April 2004 - April 2005
- 1,339 chat messages sent to the BioCoRE public help project from April 2004 - April 2005 within BioCoRE itself.

Papers citing BioCoRE: A literature search in April 2005 of the ISI Web of Science citation database yielded the following citations of the BioCoRE origin paper [83]:

- M. Dittrich, S. Hayashi, K. Schulten, "ATP hydrolysis in the beta(TP) and beta(DP) catalytic sites of F-1- ATPase." *Biophysical Journal*, 87: 2954-2967, 2004.
- I. Fudos, I. Kyriazis, "Thin client access to a visualization environment." *Lecture Notes in Computer Science*, 3039: 258-263, 2004.
- M. Dittrich, S. Hayashi, K. Schulten, "On the mechanism of ATP hydrolysis in F-1-ATPase." *Biophysical Journal*, 85: 2253-2266, 2003.
- R. Phillips, M. Dittrich, K. Schulten, "Quasicontinuum representations of atomic-scale mechanics: From proteins to dislocations." *Annual Review of Materials Research*, 32: 219-233, 2002.
- T. Finholt, "Collaboratories." *Annual Review of Information Science and Technology*, 36: 73-107, 2002.

Sites with Links to BioCoRE Site (Google, April 2005): 64 domains; 66 sites; 140 pages.

Software Evaluation

The Resource believes in close interactions with our users and in involving them in the development process through various channels. This helps to ensure the relevance of the programs, their high quality and also the loyalty of the users who realize that their voice is actively sought and seriously considered in development decisions. Mechanisms used include a standard feedback form on all software front pages (connected to the software database for quick assessment purposes), explicit encouragement to users to contact developers via email, directions on how to report bugs, user meetings, user interviews, and periodic user surveys.

The latest software surveys were conducted for NAMD and BioCoRE through March-May of 2005. Table 2 presents ratings for meeting user needs, support meeting expectations, impact on work quality, and overall satisfaction. A VMD survey is in the design stages.

A large proportion, 18%, of NAMD users has downloaded more than one version of the program. The majority of NAMD users, 86%, are affiliated with academic institutions, and most, 84%, use the program for research purposes, with 39% using NAMD for most or all of their molecular dynamics simulations. Moderate to very high levels of expertise in macromolecular modeling are reported by 72% of users, with 46% reporting similar levels of expertise in using NAMD. NIH funding supports the work of 18% of NAMD users.

Survey results indicate that the majority of BioCoRE users are affiliated with academic institutions (88%) and use BioCoRE for research purposes (71%), with a just over a third indicating research funded at least in part by NIH (37%). Most users find BioCoRE easy to use (67%), and consider themselves proficient in software use (72%). Of those respondents expressing an opinion (i.e., not answering 'unsure' on the survey), just over half (54%) indicate BioCoRE developers are responsive to their requests.

Development, Distribution, and Use of Other Software Tools and Services

Below we report service rendered by the Resource through its broad expertise in computational biology. The Resource furnished numerous software tools for biomolecular science and led its expertise in many other ways to the biomedical community.

Lending out Expertise. Additional service activities the Resource staff is engaged in are:

Total N for survey*	NAMD (770)	BioCoRE (58)
Meets needs	66%:26%:8%	64%:22%:14%
Support meets expectations	54%:40%:7%	54%:40%:7%
Positive impact on work quality	64%:30%:6%	64%:35%:2%
Satisfied overall	77%:19%:4%	72%:22%:5%
*Number of responses varies by question.	Percents are the rounded Agree%, Unsure%, Disagree% responses to survey questions	

Table 2: NAMD/BioCoRE Survey User Profiles, 2005

- MD Tools

  The Resource has developed, posted, and continually revises an MD Tools page[§] off the main web page, that describes tools used in our development efforts in three areas, simulation tools, databases, and web, programming, and administrative tools. The collection of programs, scripts, and utilities helps researchers make various modeling and simulation tasks easier, and provides basic code and utilities that can be built up into larger toolsets. In the past year, 11 new or updated packages have been added to MD Tools, all under the UIUC Open Source license, providing maximum flexibility to users.

- Visitor Program

  As part of our commitment to serve the community we host visitors[¶] and provide guidance on using our and other computational biology software. In the past year we had seven visitors and we expect more in the future. Visitors typically fund their visits, and the Resource provides computing resources and knowledge.

- User Support

  We seek to release code of high quality and with few bugs, and our local users are extremely helpful in this respect. By locally prototyping our code, major bugs are identified early on, assisting us in assuring the integrity and reliability of our products. Our user population keeps growing and consequently we are expected to invest more and more resources in user support. With over 67,000 users across our technology area[‖], support is a major task, and we take it very seriously. Our support

[§]URL:`http://www.ks.uiuc.edu/Development/MDTools/`

[¶]URL:`http://www.ks.uiuc.edu/Overview/visitor.html`

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

guidelines call for the programmers to respond to all support inquiries within 48 hours of receipt or the next business day. Nontrivial inquiries may take longer, though we strive to respond within three business days.

- Workshops

  The Resource organized three workshops on computational biophysics (see highlight on Hands-on Workshops in Computational Biophysics). A first workshop was held July 6-18, 2004 in Perth, Australia and was funded by the Institute of Advanced Studies at the University of Western Australia. The second workshop was held November 8-12, 2004 in Urbana, Illinois, and was co-sponsored by the Resource and the National Center for Supercomputing Applications. A third workshop was held December 9-5, 2004, in Boston, Massachussetts, and was funded by the National Institutes of Health. Details about each workshop, including program, participants, lectures, and materials can be found at Resource websites dedicated to the Perth[†], Urbana[‡], and Boston[§] workshops.

  The Resource has further organized three more workshops, in Lake Tahoe (May 23-27, 2005)[¶], Chicago (June 9-13, 2005)[‖], and San Francisco (June 26-30, 2005)[**]. The Lake Tahoe and Chicago workshops are funded by the National Institutes of Health, and the National Science Foundation is funding the San Francisco workshop. The workshops will be taught in a hands-on format giving participants ample opportunity to work through tutorials using real software tools. For this purpose the Resource has acquired with local funds 22 high-end laptops that are made available to participants and instructors for the duration of the workshop, each loaded with the software needed for the workshops (e.g., VMD and NAMD).

Seminars 2004-2005 In the past year we have organized and hosted 16 seminars. Our seminars are an established institution on the UIUC campus and benefit students and faculty from the Beckman Institute and other departments. We bring to our campus, with some financial support from the Beckman Institute and our NIH Resource grant, leading scientists from around the country and from all over the world. The seminars and

[†]URL:http://www.ks.uiuc.edu/Training/SumSchool/2004/

[‡]URL:http://www.ks.uiuc.edu/Training/Workshop/Urbana/

[§]URL:http://www.ks.uiuc.edu/Training/Workshop/Boston/

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

[‖]URL:http://www.ks.uiuc.edu/Training/Workshop/Chicago/

[**]URL:http://www.ks.uiuc.edu/Training/Workshop/SanFrancisco/

their respective abstracts are all posted on our web site[††] for easy information retrieval. Below is a list of the Resource seminars in the past year (mid-April 2004 - start of April 2005):

- April 8, 2004, Jeff Skolnick, Buffalo Center of Excellence in Bioinformatics, Buffalo, NY. *Prediction of Protein Structure and Function on a Proteomic Scale*
- April 21, 2004, Hui Lu, University of Illinois at Chicago, Chicago, IL. *Structure-based Modeling of Protein Binding on the Genomic Scale*
- May 3, 2004, Julie C. Mitchell, University of Wisconsin-Madison, Madison, WI. *Computer Prediction of Protein Docking and Analysis of Binding Interfaces*
- July 23, 2004, Olga Mayans, University of Basel, Basel, Switzerland. *Architectural Details of the Titin Filament - Views on the Molecular Apparatus of a Giant Machinery*
- September 13, 2004, Frank Alber, University of California, San Francisco, San Francisco, CA. *Modelling Macromolecular Assemblies: the 3D Structure of the Yeast Nuclear Pore Complex*
- September 20, 2004, Monte Pettitt, University of Houston, Houston, TX. *DNA Chips: Theory and Simulation*
- October 11, 2004, David Busath, Brigham Young University, Provo, UT. *The Simplest Ion Channels*
- October 18, 2004, Thomas C. Bishop, Tulane and Xavier Universities, New Orleans, LA. *Comparison of the Mechanical Properties Nucleosomal DNA to Free DNA*
- October 25, 2004, Alex Levine, University of Massachusetts, Amherst, MA. *The Non Linear Elasticity of an Alpha-helical Polypeptide*
- November 8, 2004, Sergei Sukharev, University of Maryland, College Park, MD. *Mechanistic Studies of Bacterial Mechanosensitive Channels*
- November 15, 2004, Aaron Oakley, Australian National University, Canberra, Australia. *Xtreme Crystallography: Atomic Resolution Structure of a Haloalkane Dehalogenase*
- November 16, 2004, Darrin M. York, University of Minnesota, Minneapolis, MN. *Simulations of Phosphoryl Transfer Reactions Using New Hybrid Quantum Mechanical/molecular Mechanical Methods*

[††]URL:`http://www.ks.uiuc.edu/Services/Seminar/`

- January 24, 2005, John E. Johnson, The Scripps Research Institute, La Jolla, CA. *Virus Particle Maturation: An Accessible Paradigm for Understanding Molecular Machines*
- January 31, 2005, Bob Eisenberg, Rush University Medical Center, Chicago, IL. *Design and Construction of Calcium Selective Channels*
- February 4, 2005, Amit Meller, Harvard University, Cambridge, MA. *Translocation and Unzipping Kinetics of DNA Molecules using a Nanopore*
- February 7, 2005, Celeste Sagui, North Carolina State University, Raleigh, NC. *New Distributed Multipole Methods for Accurate Electrostatics in Large-Scale Biomolecular Simulations*
- February 9, 2005, In-Chul Yeh, National Institutes of Health, Bethesda, MD. *Molecular Dynamics of Peptides, Nucleic Acids, and Membrane Channels*
- February 24, 2005, Emad Tajkhorshid, University of Illinois, Urbana, IL. *The Art of Water Conduction in Living Cells*
- February 28, 2005, Peter Jung, Ohio University, Athens, OH. *Ion Channel Clustering and Signal Transmission*
- February 28, 2005, Aleksei Aksimentiev, University of Illinois, Urbana, IL. *Electronic Recognition of DNA Strands with Nanopore Sensors*
- February 31, 2005, Eduardo Perozo, University of Virginia Health Sciences Center, Charlottesville, VA. *Structure and Dynamics of Ion Channels*
- March 3, 2005, Marcos Sotomayor, University of Illinois, Urbana, IL. *The Molecular Basis of Hearing*
- March 8, 2005, Saraswathi Vishveshwara, Indian Institute of Science, Bangalore, India. *Protein Structure Networks*
- March 14, 2005, David K. Lubensky, Vrije Universiteit, Amsterdam. *How to Make a Neurocrystal: Modeling the Development Patterning of the Fly's Eye*
- March 17, 2005, Elizabeth Villa, University of Illinois, Urbana, IL. *Wrestling with DNA - How Proteins Regulate the Genome*
- March 31, 2005, Melih Sener, University of Illinois, Urbana, IL. *And Then There Was Light - How Nature Harvests Sun Light*

- April 4, 2005, Mair Churchill, University of Colorado Health Sciences Center, Aurora, CO. *Throwing a Curve at DNA: Structure and Function of Chromosomal HMG Proteins*
- April 11, 2005, Cecilia Clementi, Rice University, Houston, TX. *Optimal Combination of Theory and Experiment to Explore the Protein Folding Landscape*

Training

The Resource recognizes the vital importance of training to the education and professional growth of young scientists. In the last year, the Resource has expanded training-related features and content on its web site, conducted three week or longer workshops on computational biophysics in three locations, and expanded its collection of web-accessible tutorials. Such efforts are in addition to more traditional training programs for graduate student and post-doctoral researchers, and instructional presentations about Resource software. Training opportunities provided by the Resource capitalized on a range of tools and media:

- Workshops at national and international locations
- Tutorial development and distribution (traditional and on-line)
- Presentations and lectures about Resource software
- Classes
- Graduate student education
- Visitor program

The Resource faculty are involved in programmatic instructional efforts on the UIUC campus, and in other programs in the areas of computational science and their applications on the biomedical fields and life sciences. For example, in the Fall 2004 semester, Resource faculty organized and taught a graduate-level, five-session, weekends-only course in computational biophysics.

Hands-On Workshops in Computational Biophysics

The Resource in the last year organized three 'hands-on' workshops in computational biophysics: in Perth, Australia, in June 2004, in Urbana, Illinois in November 2004, and in Boston, Massachusetts in December 2004. The workshops explored physical models and computational approaches used for the simulation of biological systems and the investigation of their function at an atomic level. The course utilized case studies including the properties of membranes and membrane proteins, mechanisms of molecular motors, trafficking in the living cell through water and ion channels, and signaling pathways. Relevant physical concepts, mathematical techniques, and computational methods were introduced, including force fields and algorithms used in molecular modeling, molecular dynamics simulations on parallel computers, and steered molecular dynamics simulations. The workshops were designed for graduate students and postdoctoral researchers in computational and/or biophysical fields seeking to extend their research skills to include computational and theoretical expertise, as well as other researchers interested in

theoretical and computational biophysics. Theory sessions in the morning were followed by hands-on computer labs in the afternoon in which students were able to set up and run simulations. Enrollment in the workshops was limited to 20 participants at each site. More detail and participant evaluation of the workshops follow below.

Supporting the 'hands-on' computational and visualization needs of the workshops required a solution that not only provided sufficient computational power, but that also provided high-quality graphics, and that was reasonably portable. The Resource purchased with local funds 22 Macintosh PowerBook G4's with 15-inch monitor displays, 80 gigabyte hard drives, and memory upgraded by Resource members to 768 megabytes. Tutorial-required software including VMD, NAMD, Mathematica, Matlab, MOE and Spartan was installed on each laptop to provide users with easy access to these tools when working on the tutorials. Files required by the tutorials were also installed on the hard drive, as were instruction and copies of the tutorial texts. Peripheral devices to support use of the laptops included optical mice, cable locks for security, two custom-designed cases for transporting the laptops, a portable projector, a wireless base station to provide Internet access to the laptops where needed, and two 160 gigabyte firewire hard drives as backup of all hard drive materials. At each workshop, teaching assistants set up the laptops for the 20 participants, with the remaining two laptops used by the instructors for demonstrations and leading participants through lectures and tutorials. In this fashion, all participants were provided with needed learning resources, without the workshop having to rely on the availability of computer labs in various locations.

Perth Workshop. A two-week event, the Perth workshop ran from June 7-18, 2004, and was sponsored by the University of Western Australia's Institute for Advanced Studies. Taught by two Resource faculty (Klaus Schulten, Zan Schulten) with support from three graduate student assistants, the workshop introduced participants via lectures to topics such as an introduction to bioinformatics and modeling large systems. After the daily lectures, participants worked through tutorials on VMD, NAMD, and other topics related to the lectures and involving Resource and other software programs. The 27 participants in the workshop were a highly educated group; all had a doctoral degree or were PhD candidates, with the exception of four Masters students. An evaluation at the end of the workshop indicated that 95% agreed that the workshop broadened their understanding of the concepts and principles of theoretical and computational biophysics, and again 95% agreed that the workshop improved their ability to carry out original research in the field of theoretical and computational biophysics. All materials developed for this workshop, as well as evaluation results, can be found at the Resource website dedicated to this workshop*.

*URL:`http://www.ks.uiuc.edu/Training/SumSchool/2004/`

Urbana Workshop. Co-sponsored by the Resource and the National Center for Supercomputing Applications[†], the workshop was held at the Beckman Institute for Advanced Science and Technology, in Urbana, Illinois, from November 8-12, 2004. The workshop included lectures from three Resource faculty (Klaus Schulten, Zan Schulten, and Emad Tajkhorshid), tutorial support from the majority of Resource graduate students, and included topics such as steered molecular dynamics and parameters of classical force fields. The twenty workshop participants, while mostly from the United States, also came from Europe and Asia, represented academia, governments, and industry, and were selected from a pool of nearly 60 applicants. Evaluation results again found a majority, 76%, agreeing the workshop broadened their understanding of theoretical and computational biophysics, and similarly 87% indicated the workshop improved their ability to carry out original research in theoretical and computational biophysics. Greater detail on the workshop is available at the web site the Resource has devoted to the Urbana workshop[‡].

Boston Workshop. A third workshop was held December 5-9, 2004, in Boston, Massachusetts, with lectures and tutorial support provided by two Resource faculty (Klaus Schulten, Emad Tajkhorshid) and three graduate student teaching assistants. Funding was provided via a grant from the National Institutes of Health. Among the topics covered were protein structure and dynamics and simulating membrane channels. Twenty participants, including eight with doctorates, were selected from over 50 applicants from nations around the world. The workshop format again followed morning lectures with afternoon tutorial work in labs as facilitated by the prepared laptops. Evaluation results are again quite positive, with 95% and 90% of participants agreeing that the workshop broadened their understanding of theoretical and computational biophysics and improved their ability to carry out original research in theoretical and computational biophysics respectively. Greater detail on the workshop is available at the web site the Resource has devoted to the Boston workshop[§].

Future Workshops. The Resource continues its dedication to training by organizing three more workshops: One in Lake Tahoe (May 23-27, 2005)[¶], with funding from the National Institutes of Health; another in Chicago (June 9-13, 2005)[‖], again funded by the National Institutes of Health; and, a third workshop in San Francisco (June 26-30, 2005)[**], using

[†]URL:http://www.ncsa.uiuc.edu/

[‡]URL:http://www.ks.uiuc.edu/Training/Workshop/Urbana/

[§]URL:http://www.ks.uiuc.edu/Training/Workshop/Boston/

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

[‖]URL:http://www.ks.uiuc.edu/Training/Workshop/Chicago/

[**]URL:http://www.ks.uiuc.edu/Training/Workshop/SanFrancisco/

funding provided by the National Science Foundation[††].

Tutorials

Originally, a set of six tutorials - providing instruction on VMD, NAMD, and various relevant scientific topics - were developed by the Resource for a 2003 summer school. Since that point, the Resource has devoted extensive resources not only to the maintanance and update of these tutorials, but to the development of new tutorials for use in workshops and independent study. Tutorials generally include a central document with text, screen captures and images, and directions for the software package(s) needed to complete the tutorial. As needed, directories of files required for the tutorials are provided. The Resource is presently translating the tutorials to assure they work on mulitple platforms (i.e., not only on the Mac plaform, but also on Windows and Linux), which will greatly expand the utility and availability of the tutorials. Currently, the Resource web site provides twelve tutorials (including two developed by external authors) as listed below[‡‡]:

VMD Tutorials

- VMD Molecular Graphics
- Aquaporins with the VMD MultiSeq Tool
- Visualization and Analysis of CPMD data with VMD

NAMD Tutorials

- NAMD Tutorial
- A Tutorial to Set Up Alchemical Free Energy Perturbation Calculations in NAMD
- Building Gramicidin A

Science Tutorials

- Parameterizing a Novel Residue
- Evolution of Protein Structure Aspartyl-tRNA Synthetase
- Sequence Alignment Algorithms
- Topology File Tutorial

[††]URL:`http://www.nsf.gov/`

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

- Stretching Deca-Alanine
- Simulation of Water Permeation through Nanotubes

Software Presentations. In the past year, presentations and tutorials on Resource software have been presented at conferences, meetings, and at the Resource workshops, as below[†]:

- February 2005, Urbana, IL, Beckman Institute - Imaging Technology Group Forum, *Dancing Proteins: 3-D Visualization of Protein Structure and Dynamics on Next-Generation Graphics Hardware* (John Stone)
- February 2005, University of Missouri at Rolla, Rolla, MO, Department of Computer Science CS Colloquium, *Dancing Proteins: 3-D Visualization of Protein Structure and Dynamics on Next-Generation Graphics Hardware* (John Stone)
- February 2005, Purdue University, West Lafayette, IN, Envision Center, *Dancing Proteins: 3-D Visualization of Protein Structure and Dynamics on Next-Generation Graphics Hardware* (John Stone)
- December 2004, Nance, France, INRIA/CNRS ARC Docking Project, *VMD Biomolecular Visualization and Analysis* (John Stone)
- December 2004, Boston, MA, 'Hands-on' Workshop in Computational Biology *VMD Molecular Graphics tutorial* (Resource staff) *NAMD Molecular Dynamics tutorial* (Resource staff)
- November 2004, Pittsburgh, PA, IEEE/ACM SC2004 Conference, *Exploring Biomolecular Machines with Supercomputers* (James Phillips)
- November 2004, Urbana, IL, 'Hands-on' Workshop in Computational Biology - *VMD Molecular Graphics tutorial* (Resource staff) -*NAMD Molecular Dynamics tutorial* (Resource staff)
- October 2004, Arlington, VA, NSF Cyberenabled Chemistry Workshop, *BioCoRE* (Kirby Vandivort)
- June 2004, Perth, Australia, 'Hands-on' Workshop in Computational Biology - *VMD Molecular Graphics tutorial* (Resource staff) -*NAMD Molecular Dynamics tutorial* (Resource staff)

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

Training on the Web. The Resource continues to make available to the biomedical community a variety of training resources via the Resource web site and other Resource channels:

Learning materials and details from each workshop are provided in web sites devoted to each worskhop site, including links to lecture and tutorial files, allowing visitors to access the content of each workshop. Two web sites are devoted to tutorials posted by the Resource, one providing a complete list of all tutorials, the other listing only those used in workshops, a useful organization for those who want to see all relevant tutorials or just review workshop content.

BioCoRE continues to be a valuable tool for training support. The collaboratory was used to support a graduate-level course in non-equilibrium statistical mechanics, with students, instructors, and some Resource staff all participating in a BioCoRE project created specifically for the class. BioCoREs chat tool supported interaction among project members, and the message board served as a posting board for notices about the class such as homework releases and due dates. A new feature of BioCoRE allowed the message board entries to also be e-mailed to students. Homework assignments, class lectures, and tutorials were made available to students via BioCoREs file system, the BioFS. A parallel administrative project was also created in BioCoRE, and limited to instructional and Resource staff, as a means of coordinating course materials and course organization.

Resource Library. In the past year, 40 new books have been purchased to expand the Resource's already well-stocked library. To supplement the UIUC library's collection of on-line and print journals, the Resource subscribes to the following journals in the sciences and computing:

- Physics Today
- Science
- Sys Admin
- Journal of NIH Research
- C/C++ Users Journal
- Dr. Dobb's Journal
- Linux Journal
- Nature
- Nature Structural Biology

Graduates. Recent UIUC graduates and postdoctoral associates who received their training at the Resource are:

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

- Chalermpol Kanchanawarin Ph.D., Physics, University of Illinois, Spring 2005
- Sameer Kumar Ph.D., Computer Science, University of Illinois, Spring 2005
- Wei Wang Ph.D., Computer Science, University of Illinois, Spring 2005
- Markus Dittrich Ph.D., Physics, University of Illinois, Spring 2005

Postdoctoral Associates

- Dr. Aleksei Aksimentiev
- Dr. Alexander Balaeff
- Dr. Rosemary Braun
- Dr. Melih Sener

Visitors. Now in its eighth year, the Resource visitor program[†] provides young scientists the opportunity to receive on-site training with Resource members, with stays ranging from a week to several months. Visitors, who come with their own support, learn how to use Resource produced software and other software packages hosted on Resource computers, and benefit from the expertise and knowledge of Resource members. By the conclusion of their visit, visitors have acquired critical skills and new experiences that they can take back to their home laboratories.

While this effort-intensive initiative can be quite taxing on Resource members, the visitor initiative provides practical, useful knowledge to visitors, and serves as a vehicle for transferring knowledge back to the biomedical community. Visitors during the last year include:

- Itamar Kass, Biological Chemistry, Hebrew University of Jerusalem (March 2005)
- Basak Isin, Computational Biology, University of Pittsburgh (February 2005)
- Michael Hoffman Theoretical Physics, Universitaet Paderborn, Germany (Fall 2004)

[†]URL:`http://www.ks.uiuc.edu/Overview/visitor.html`

- Peter Freddolino, Biology, California Institute of Technology (March 2004)
- Joel Hirsch, Biochemistry, Tel Aviv University (August 2004)
- Christopher Chipot, Physical Chemistry, Universite Henri Poincare, France (September 2004)
- Jerome Henin, Physical Chemistry, Universite Henri Poincare, France (November 2004)

Training Collaborations. In cooperation with the World Universities Network (WUN) exchange program, meant to foster international interactions between students and senior researchers in the field, the Resource assisted in the conversion of a May, 2004 lecture given by Klaus Schulten to an on-line, streaming lecture accompanied by lecture slides, available at the WUN website[†] and listed at the Resource website.

Manuals and Tours. Our software manuals have been available on the web for many years, and are regularly updated. Users of VMD wanting to learn how to modify software, write their own plugins, or otherwise extend VMD can now access a completely revised programmers guide, utilizing a new source-level documentation system called "Doxygen" that is updated nightly on the VMD website.[†] The NAMD manual and NAMD-L mailing list are now searchable via the application's website,[‡] a useful tool for users looking to find needed information without extensive browsing of documents. Also in use is the NamdWiki[§], a user-editable web site that contains 59 customized pages, providing a public whiteboard for sharing NAMD issues and experience. In particular, a general troubleshooting page lists symptoms and solutions for common error messages encountered during runs, and there are pages with advice for building and running NAMD on a specific platform. The BioCoRE tour,[¶] that combines a tutorial with slides indicating software features and depicting their utilization, has been updated to display new features, such as the revised interface and the polls/quizzes tool. The tour is regularly updated and developed. Similarly, BioCoRE documentation has been updated to include information on changes to the WebDAV file system, themes for the new interface, and new screen captures have been added for the VMD Pub/Synch tool.

[†]URL:`http://www.shef.ac.uk/learningmedia/dm/schulten/lecture.html`

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

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

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

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

Dissemination

The Resource's broadscale dissemination and outreach efforts continued through the last funding period, taking advantage of a variety of delivery mechanisms from web-based distribution of Resource-produced papers and know-how, through talks in meetings, workshops and conferences, software distribution, news stories and press releases, demonstrations, and to the use of Resource-made images in a variety of third-party publications and presentations.

The Resource published brochures, numerous academic articles, and was also featured for its accomplishments in a variety of printed and online media. For example, an image of water permeating through aquaporin produced by Resource faculty members Emad Tajkhorshid and Klaus Schulten, was the winning illustration in the 2004 Visualization Challenge as sponsored by *Science* magazine and the National Science Foundation*. Subsequently, the victory was mentioned by numerous local and national organizations (see list of news stories below).

Stories on the Resource appeared in popular media, scientific journals, online news sources, and more. All news-making stories are documented at the Resource web site at the "In the News" section†:

- Daviss, B. (2005, January 17). Building High-speed Lanes on the Information Highway. *The Scientist*. http://www.the-scientist.com/2005/1/17/24/1
- Staff. (2005, January 8). Going Against the Flow. *UIUC Department of Physics*. http://www.physics.uiuc.edu/Research/Highlights/against-the-flow.htm
- Staff. (2004, December). Flip-flopping molecules. *UIUC College of Liberal Arts & Sciences: Alumni & Friends LAS News*. http://www.las.uiuc.edu/news/2004fall/04december_aquaporin.html
- Cho, A. (2004, December 6). Winning an Uphill Battle. *Physical Review Focus*. http://focus.aps.org/story/v14/st23
- McGaughey, S. (2004, November 16). Computational Biophysics Workshop popular. *Beckman Institute News Bureau*. http://www.beckman.uiuc.edu/news/featured/TCBworkshop.html

*URL:`http://www.sciencemag.org/cgi/content/full/305/5692/1905`

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

- Kline, G. (2004, October). UI scientists have a winning wet look. *The News-Gazette Online*.
  http://www.news-gazette.com/localnews/story.cfm?Number=16970

- Frankel, F. (2004, November-December). Watching Water Channels. *American Scientist Online*, 92(6).
  http://www.americanscientist.org/template/AssetDetail/assetid/37229;_ONFDOaC

- Staff. (2004, October 1). U of I Scientists Recognized for Best Computer Visualization. *UIUC Engineering at Illinois News Archive*.
  http://www.engr.uiuc.edu/research/news/index.php?xId=063708640798

- Staff. (2004, September 27). NCSA user Schulten earns visualization award. *NCSA Access News Brief*.
  http://access.ncsa.uiuc.edu/Briefs/2004-09-27NCSA_user.html

- Staff. (2004, September 27). Science as Art: Competition sponsored by Science and NSF honors beauteous science. *Chemical and Engineering News*, 82(39), p. 6.
  http://pubs.acs.org/cen/news/8239/8239notw3.html

- Grimm, D. (2004, September 24). The Winners - 2004 Visualization Challenge: Illustration. *Science*, 305(5692, 1905).
  http://www.sciencemag.org/cgi/content/full/305/5692/1905

- Staff. (2004, September 23). Science and Engineering Visualization Challenge - Results 2004 (Illustration, First Place). *National Science Foundation Office of Legislative and Public Affairs*.
  http://www.nsf.gov/news/special_reports/scivis/results.jsp

- Zech, C. (2004, September 23). Beckman Institute expert wins Science magazine contest for best visualization. *University of Illinois at Urbana-Champaign News Bureau*.
  http://www.news.uiuc.edu/news/04/0923visualization.html

- Schneider, M. (2004, August 13). Protein Motors Incorporated: With PSC's Jonas, an exceptional machine for quantum computations, researchers attacked a key problem in protein biology. Projects in Scientific Computing. *Annual Research Report of the Pittsburgh Supercomputing Center*.
  http://www.psc.edu/science/2004/schulten/

- Lazou, C. (2004, April 5). HPCx Industry Day at CCLRC Daresbury Laboratory. *EnterTheGrid - Primeur*.
  http://www.hoise.com/primeur/04/articles/monthly/CL-PR-05-04-2.html

Publications In the past year Resource members have published and/or submitted or presented:

- 34 articles in refereed journals (7 in press)
- 41 talks by PIs, 19 talks or meetings attended by other Resource members
- 17 posters

Lectures and Talks

The Resource PIs gave the following talks in the last 12 months[‡]:

Klaus Schulten

- April, 2004, Washington, DC, NSF/EPSRC US/UK Workshop *HPC and Grid Computing for Biomolecular Modeling of Membrane Processes* (with Diane Lynch)
- April 2004, Chicago, IL, Witnessing in front of the Energy Department, BESAC Subcommittee Meeting *Software Development in Computational Biology*
- May 2004, Tempe, AZ, NSF Workshop on the Role of Theory in Biological Physics and Materials *Plenary Lecture*
- May 2004, Santa Fe, NM, 24th Annual Conference of the Center for Nonlinear Studies *Mechanical Functions of Proteins*
- May 2004, Urbana, IL, WUN Bioinformatics on line Video Seminar Series *Physical Bioinformatics: A Case Study*
- June 2004, Perth, Australia, 2004 Summer School in Computational Biophysics
  - *Introduction to Molecular Dynamics in Biological Systems*
  - *Computational and Theoretical Biophysics*
- June 2004, Washington, DC, P41 Investigator Meeting *Towards Understanding Membrane Channels*
- July 2004, San Diego, CA, JASONs Meeting *Computational Biophysics*
- August 2004, UIUC , Urbana, IL, Biophysics & Computational Biology Non-MCB Faculty Talks *Theoretical Biophysics*

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

- August 2004, Philadelphia, PA, 228th ACS National Meeting and Exposition *Single Molecule Electrical Recordings Through Artificial Nanopores, an Experimental - Computational Study*
- August 2004, Irvine, CA, Arnold and Mabel Beckman Foundation, Future Initiatives Conference *Biological and Synthetic Nanopores for Single Molecule Sorting and Recording*
- September 2004, UIUC, Urbana, IL, Applied Math Seminar *Conceptual and Mathematical Challenges in Computational Biology*
- September 2004, Golden, CO, 2004 NREL Computational Biology Workshop *Towards Understanding Membrane Channels*
- October 2004, UIUC, Urbana, IL, Physics Faculty Retreat *Theoretical and Computational Biophysics*
- October 2004, UIC, Chicago, IL, Symposium on Computational Science of Biomolecules; Applications in Medicine and Therapeutics *Physical Bioinformatics: A Case Study*
- October 2004, UIUC, Urbana, IL, Molecular and Electronic Nanostructures Program Review *Theoretical and Computational Biophysics*
- October 2004, New York, NY, D. E. Shaw Research and Development Seminar Series *Biomolecular Modeling Today*
- November 2004, UIUC, Urbana, IL, Physics Advisory Board Meeting *Theoretical and Computational Biophysics*
- November 2004, Irvine, CA, Physics Department Colloquium at UC-Irvine *The Physics of Biological Channels*
- November 2004, Urbana, IL, 'Hands-on' Workshop in Computational Biology
  - *Introduction to Protein Structure and Dynamics*
  - *Statistical Mechanics of Proteins*
- December 2004, Houston, TX, University of Texas Science Center, The John P. McGovern Lectureship in Biomedical Computing and Imaging *Computational Bio- and Nanoscience*
- December 2004, Boston, MA, 'Hands-on' Workshop in Computational Biology
  - *Introduction to Protein Structure and Dynamics*
  - *Introduction to Bioninformatics*

  - *Statistical Mechanics of Proteins*

- February 2005, Long Beach, CA, Biophysical Society 2005 Annual Meeting *Molecular Dynamics Study of Membrane Channel Gating*

- March 2005, Urbana, IL, Biophysics Recruiting Weekend *Modeling Cellular Processes*

- April 2005, West Lafayette, IN, Purdue University, 100 Years of Physics Accomplishments - "Grande Finale" Symposium *The Future of Biological Physics*

Laxmikant Kale

- April 2004, Santa Fe, NM, CAC Workshop at IPDPS 04

  - *Opportunities and Challenges of Modern Communication Architectures: Case Study with QsNet*
  - *BigSim: A Parallel Simulator for Performance Prediction of Extremely Large Parallel Machines*
  - *Performance Modeling and Programming Environments for Petaops Computers and the Blue Gene Machine*

- May 2004, Siebel Center, UIUC, Urbana, IL, *Interactive Molecular Dynamics in Parallel Supercomputers*

Emad Tajkhorshid

- June 2004, Chicago, IL, Department of Medicine, University of Chicago *Selective Transport of Substrates across Biological Membranes: Lessons from Computational Studies of Membrane Channels*

- September 2004, Heidelberg, Germany, International Symposium on Retinal Proteins: Experimental and Theory *Mechanism of Storage of Light Energy in Rhodopsins*

- September 2004, Freiburg, Germany, Annual Meeting of the German Biophysical Society *Novel Mechanisms of Substrate Selectivity in Membrane Channels*

- November 2004, Urbana, IL, 'Hands-on' Workshop in Computational Biology *Simulating Membrane Channels*

- December 2004, Boston, MA, 'Hands-on' Workshop in Computational Biology

  - *Parameters for Classical Force Fields*

  - *Simulating Membrane Channels*

- February 2005, Long Beach, CA, Biophysical Society 2005 Annual Meeting
  - *Structural evidence for asymmetric function of passive membrane channels*
  - *Role of water in transient cytochrome c2 docking*
- February 2005, Urbana, IL, Beckman Institute, 4D Nanostructure Lecture Series *The Art of Water Conduction in Living Cells*

Other Resource members gave the following presentations, talks, poster presentations, or attended meetings in the past year:

- April 2004, Santa Fe, NM, *IPDPS Conference* (Sameer Kumar, Gengbin Zheng)
- May 2004, Santa Fe, NM, *Statistical Physics of Macromolecules* (Jin Yu)
- May 2004, Siebel Center, UIUC, Urbana, IL, *Interactive Molecular Dynamics in Parallel Supercomputers* (Jordi Cohen, Jay Desouza, Gengbin Zheng)
- May 2004, Argonne, IL, APS Users Meeting *Solution X-Ray Scattering from Nanoscale Phospholipid Bilayer - Protein Systems* (Amy Shih)
- June 2004, Proctor Academy, Andover, NH, Gordon Research Conference on Molecular and Cellular Bioenergetics (Markus Dittrich) *Insights into the molecular mechanism of ATP synthase*
- June 2004, Frauenchimsee, Germany, 11th International Conference on Retinal Proteins *Molecular dynamics simulation of bacteriorhodopsin's photoisomerization using ab initio forces for the excited state chromophore* (Shigehiko Hayashi)
- August 2004, Philadelphia, PA, American Chemical Society Meeting - Biophysical Chemistry and Novel Imaging of single Molecules and Single Cells *Single Molecule Electrical Recordings with Artificial Nanopores* (Aleksei Aksimentiev)
- October 2004, Arlington, VA, NSF Cyberenabled Chemistry Workshop, *BioCoRE* (Kirby Vandivort)
- November 2004, Pittsburgh, PA, IEEE/ACM SC2004 Conference, *Exploring Biomolecular Machines with Supercomputers* (James Phillips)
- December 2004, Nance, France, INRIA/CNRS ARC Docking Project, *VMD Biomolecular Visualization and Analysis* (John Stone)
- February 2005, Long Beach, CA, Biophysical Society 49th Annual Meeting

- *Molecular dynamics simulations of nuclear pore FG repeat proteins binding to importin-beta* (Tim Isgro)
- *Computational Study of the Chemo-Mechanical Coupling and ATP Hydrolysis in F1-ATPase* (Markus Dittrich)
- *Modeling the Polarizability of Carbon Nanotube Molecular Channels* (Deyu Lu)
- *Molecular Dynamics Study of an Integrin Ligand Complex* (Mu Gao)
- *Microscopic Kinetics of DNA translocation through synthetic nanopores* (Aleksij Aksimentiev)
- *Stretching DNA using artificial Nanopore* (Aleksij Aksimentiev)
- *Imaging the Permeability of alpha-Hemolysin with Molecular Dynamics* (Aleksij Aksimentiev)
- *Molecular Dynamics Study of Mechanosensation Proteins Ankyrin and Cadherin* (Marcos Sotomayor)
- *Multiscale Modeling of Gating and Ion Conduction in the Mechanosensitive Channel of Small Conductance MscS* (Marcos Sotomayor)
- *Molecular dynamics studies of nucleotide gated ion channel activity of aquaporin-1* (Jin Yu)
- *Molecular Modeling and Dynamics Studies of GB1 Protein Fibril* (Eric Lee)
- *Molecular dynamics simulations of discoidal bilayers assembled from truncated human lipoproteins* (Amy Shih)
- *Molecular dynamics study of substrate permeation and selectivity in E. coli aquaporins GlpF and AqpZ* (Yi Wang)
- *Evolution of Excitation Transfer Pathways of Photosystem I from Cyanobacteria to Plants* (Melih Sener)
- *Molecular dynamics simulations of spontaneous and forced motions of isolated subunits of F1-ATP synthase* (Barry Isralewitz)
- *Mechanical Interactions between Lac Repressor and DNA Loops* (Elizabeth Villa)
- *Molecular Dynamics Study of KvAP Gating* (Fatemeh Khalili)

- February 2005, Urbana, IL, Beckman Institute - Imaging Technology Group Forum, *Dancing Proteins: 3-D Visualization of Protein Structure and Dynamics on Next-Generation Graphics Hardware* (John Stone)

- February 2005, University of Missouri at Rolla, Rolla, MO, Department of Computer Science CS Colloquium, *Dancing Proteins: 3-D Visualization of Protein Structure and Dynamics on Next-Generation Graphics Hardware* (John Stone)

- February 2005, Purdue University, West Lafayette, IN, Envision Center, *Dancing Proteins: 3-D Visualization of Protein Structure and Dynamics on Next-Generation Graphics Hardware* (John Stone)
- March 2005, Urbana, IL, Beckman Institute Open House 2005
  - *Wrestling with DNA - How Proteins Regulate the Genome* (Alexander Balaeff)
  - *Wrestling with DNA - How Proteins Regulate the Genome* (Elizabeth Villa)
  - *The Molecular Basis of Hearing* (Marcos Sotomayor)
  - *DNA Inside a Nanopore* (Eduardo Chu-Cruz, Alek Aksimentiev)
  - *Nanodisc* (Amy Shih)
  - *Nano-soccer* (Deyu Lu)

Outreach

The broad outreach efforts of the Resource continue, reaching ever more members of the biomedical community due to our increasing visibility on the web, in the software user community, in meetings, journals, and other media. Telling indicators demonstrating the impact of our outreach activities include:

- Major sites with links to our site
- Major sites that use our images
- Others publish our images
- On-site demonstrations

There have been 423,243 unique visitors to the Resource web site, an average of 44,672 per month, over the last year; also, 985.2 gigabytes was downloaded from the site. The sections most visited are shown in Table 3.

A recent Google search (April, 2005) yielded the following statistics regarding external sites that link to the main Resource web page: 915 pages link to the main page, from 67 sites, registered under 65 different domains. Example education, scientific resources, and programming or computing-related sites with links to the Resource web site are provided below:

Education:

- *Cornell University: Biology Department, Molecular Biology and Genetics Department, Physics Department, Computer Science Department, and Medical Library*
  bio.cornell.edu, www.mbg.cornell.edu, www.physics.cornell.edu, www.cs.cornell.edu, library.med.cornell.edu

	Total Visitors	Visitors per Month
VMD	149,082	16,233
NAMD	60,722	7,013
BioCoRE	18,673	2,140
Other Research	84,901	7,075
Galleries	28,590	2,759
Papers	25,449	2,945
Seminars	3,715	553

Table 3: Numbers from April 2004 – March 2005

- *University of California at San Diego: Physics Department, Chemistry Department, Keck Lab for Integrated Biology, and McCammon Biophysics Group*
  physics.ucsd.edu, www-chem.ucsd.edu, keck2.ucsd.edu, mccammon.ucsd.edu
- *University of California at Berkeley: Electron Microscopy Group, Computer Science Department, Astronomy Department, and Molecular Graphics and Computation Facility*
  cryoem.berkeley.edu, www.cs.berkeley.edu, astron.berkeley.edu, glab.cchem.berkeley.edu
- *Purdue University: Computer Science Department, Chemistry Department, Nanotechnology Simulation Hub, and Instructional Computing Services*
  www.cs.purdue.edu, www.chem.purdue.edu, www.nanohub.purdue.edu, expert.ics.purdue.edu
- *Duke University: Biology Department, Electrical Engineering Department, and Single Molecule Force Spectroscopy Lab*
  www.biology.duke.edu, www.ee.duke.edu, smfs.pratt.duke.edu
- *New York University: Math Department, Computer Science Department, and Computational Biology/Chemistry/Biomathematics Department*
  www.math.nyu.edu, www.cs.nyu.edu, monod.biomath.nyu.edu
- *Harvard University: Instructional Computing Group, Wagner NMR Structural Research Group, and Molecular Biology Core Facilities*
  www.courses.fas.harvard.edu, gwagner.med.harvard.edu
- *Massachusetts Institute of Technology: Open Courseware Project and Computer Graphics Group*
  ocw.mit.edu, graphics.lcs.mit.edu

- *Scripps Research Institute: Amber Molecular Dynamics and Metalloprotein Database*
  amber.scripps.edu, metallo.scripps.edu
- *Stanford University: Medical Informatics and Computer Science*
  www.smi.stanford.edu, www-cs-students.stanford.edu
- *Yale University: Center for Structural Biology and Database of Macromolecular Movements*
  www.csb.yale.edu, molmovdb.mbb.yale.edu
- *University of Pennsylvania: Engineering Department and Center for Molecular Modeling*
  www.seas.upenn.edu, www.cmm.upenn.edu

Scientific Resources:

- *Protein Data Bank*
  www.rcsb.org
- *Biophysical Journal*
  www.biophysj.org
- *Science Magazine*
  www.sciencemag.org
- *Nature Magazine*
  www.nature.com
- *Howard Hughes Medical Institute*
  www.hhmi.org
- *Slashdot*
  science.slashdot.org
- *Chemistry at Harvard Molecular Mechanics*
  www.charmm.org
- *GROMACS Molecular Dynamics*
  www.gromacs.org
- *CPMD consortium*
  www.cpmd.org
- *Prentice Hall*
  wps.prenhall.com

- *The Foresight Institute Nanotechnology*
  www.foresight.org
- *PhysicsWeb, Physics News and Resources*
  physicsweb.org
- *Bioinformatics Open-Access*
  bioinformatics.org
- *Physical Review Focus*
  focus.aps.org
- *Computational Chemistry List*
  www.ccl.net
- *American Scientist Magazine*
  www.americanscientist.org
- *Microbiology Information Portal*
  www.microbes.info
- *Free Science*
  freescience.info
- *Protein Society*
  www.proteinsociety.org
- *Ernest Orlando Lawrence Berkeley National Laboratory*
  www-vis.lbl.gov/
- *Center for Molecular Modeling at National Institutes of Health*
  cmm.info.nih.gov

Programming/Computing Related:

- *Apple Computers*
  www.apple.com
- *OpenGL Programming*
  www.opengl.org
- *Silicon Graphics*
  www.sgi.com

- *Linux Online*
  www.linux.org
- *Java 3D Community*
  www.j3d.org
- *GNU Operating System*
  www.gnu.org
- *PovRay Objects Collection*
  objects.povworld.org
- *VersionTracker Software Downloads*
  www.versiontracker.com
- *FreshMeat Software Downloads*
  www.freshmeat.net
- *Codebeach Developer's Guide*
  www.codebeach.com
- *Sourceforge Open Source*
  sourceforge.net
- *StereoGraphics*
  www.stereographics.com
- *FreeBSD Online*
  www.freebsd.org
- *Beowulf Clusters*
  www.beowulf.org
- *Freeware Web*
  www.freewareweb.com/

The Resource responds about twice a month (21 total in the last year) to requests for permissions to use Resource images on other sites, in textbooks, papers, and talks given or written by others. A formulated a standard response gives answer to such requests while protecting our copyrights and ownership though the Resource has adopted an open and liberal approach in granting such permissions.

Brochures Two brochure projects were undertaken by the Resource as a means of communicating information about our programs, research, and software. Each brochure is described below; and completed brochures can be found online at the Resource website[§]:

- *VMD/NAMD/BioCoRE Brochure* - describes the main features and benefits of VMD, NAMD, and BioCoRE on single brochure, informing readers of not only the benefits of a single program, but also alerting them to the other software applications produced by the Resource.
- *Bringing Computing to Life* - currently under development, the brochure will describe the challenges and work culture of the developers who produce VMD, NAMD, and BioCoRE, as well as the system that supports their efforts.

[§]URL:`http://www.ks.uiuc.edu/Gallery/Brochure/`

Licensing and Distribution

The Resource maintains ongoing discussions with the UIUC Office of Technology Managment, industry, and others to develop licenses that allow broad distribution of our software. In the last year, the Resource provided 24 software disclosures from the MDTools compilation to the UIUC Office of Technology Management, with an emphasis that the university place all of these tools under an open-source license. Further, the Resource took a significant step forward in licensing, by developing a license allowing for a commercial distribution of NAMD. In cooperation with the UIUC Office of Technology management, the Resource negotiated a non-exclusive distribution license with Scienomics[¶], a software and services company in the area of molecular modeling that is based in Paris, France. The license allows Scienomics to distribute an unmodified copy NAMD as part of their central software package, titled "Materials and Processes Simulations" or "MAPS", with a small fee returned for each distribution. The Resource is not obligated to provide additional or unique support as part of the contract, and the distribution does not invalidate the current NAMD license for those using the software via the MAPS program. It is hoped this contract will provide a foundation for future, similar distribution opportunities.

[¶]URL:http://www.scienomics.com/

The Resource advisory board met this year on May 16, 2005, and produced the following report. The Advisory Board was composed of the following members:

- Dr. Greg Farber, Program Officer, National Institutes of Health
- Dr. Angel Garcia, Department of Physics, Applied Physics and Astronomy, Rensselaer Polytechnic Institute
- Dr. Gerhard Klimeck, Technical Director, Network for Computational Nanotechnology, Purdue University
- Dr. Angela Gronenborn, Group Leader, National Institutes of Health
- Dr. Benoit Roux, Department of Biochemistry and in the Department of Physiology and Biophysics, Weill Medical College of Cornell University (Chair)
- Dr. Gila Budescu, Assistant Director for Research and External Affairs, Institute for BioNanotechnology in Medicine, Northwestern University

Advisory Board Report, May 16, 2005

NIH Resource FOR Macromolecular Modeling AND Bioinformatics

Summary

The report on the Resource from the past year was very impressive. By any standards, this is a fantastic usage of NCRR resources, with world-leading quality in computational modeling and software development. The PI briefly reported on the activity of the seven components: VMD, NAMD, BioCoRE, collaborations, training, service, and dissemination. All components show very strong activities. Some, such as VMD and NAMD, have clearly a very high impact in the scientific community. The BioCoRE, a program for grid computing and research management, seems to be reaching a mature level where its main features could be of great usage for collaborative projects that require sharing of large (and precious) datasets. The PI gave a perspective on a planned future development called HPBS for "high productivity biomodeling suite", which will link several biomolecular modeling tools into a unified and modular environment. Collaborations, particularly with high profile experimentalists, have been spectacular in the last year. Excellent training workshops have become increasingly popular and have a good attendance. Additional space at the Beckman Institute to allow for visitors to stay and train on site will have a great positive impact. Apparently, this much-needed space will soon be available and that should be very helpful. In terms of the services and dissemination, it is difficult to imagine how the TCBG could do more with the increasing demands by the large number of users of VMD and NAMD. So far, the services provided have been

impeccable, though this is clearly beginning to put more pressure on the TCBG. In the following, we go into more detail about each of the components.

1. VMD

The advisory board unanimously feels that VMD is an extremely popular program and its success is based on a number of appealing features, not the least its ease of use. Now there exists an exciting development plan, namely, the inclusion of multiple (superposition) views and sequence analysis. This is an important and topical extension of the capabilities. The successful implementation of these novel capabilities reflects the efforts by Zan Luthey-Schulten and coworkers; their inclusion into the renewal proposal was a pivotal and shrewd choice. The new sequence analysis feature of VMD is a tremendous asset. It is important that these features make it into the next release of VMD this will generate a large number of new users and expand the user community into the large number of molecular biologists. On the graphics and structure/dynamics side, VMD has also seen major improvements such as a new cartoon representation that yields high quality images for publication purposes. VMD will also take advantage of new graphics advances, for example, through programmable shading or through serving 64 bit processors that permit analysis of many gigabytes of structural data as needed for trajectory analysis. VMD now is capable of loading the entire protein data bank (over 30 Gigabytes) in one session allowing for previously unimaginable opportunities for structure comparisons.

VMD as a Broad Tool in Molecular Cell Biology

VMD is not simply a structure viewing tool; it is able to load, display, and manipulate biological structure and sequence information, as well as other diverse data such as quantum mechanical electronic orbitals and cryoelectron microscopy images, Because of its plug-in-driven input and output, it is currently able to interoperate with all major modeling tools, and these capabilities are continually expanding. VMD is designed to streamline the creation of high quality images, and to allow for easy manipulation of the image for analytical purposes, including current development on allowing multiple simultaneous viewpoints of a molecule. Because of its versatility and easy scripting interface, VMD can be used not only as a visualization tool, but rather as a central platform for many diverse analytical tasks on biological systems. This is a major strength and the inclusion of such diverse biological data will open the Resource to a wider and new constituency.

VMD Supporting Modelers

VMD has traditionally been a tool for modelers since it offers a wide variety of tools to generate and prepare systems for simulations. Biomolecules can be solvated or embedded in lipid membranes and VMD's flexible plug-in mechanism allows the user to create custom tools for problem specific needs. Simulation trajectories of systems exceeding

1million atoms can be efficiently displayed, managed, and analyzed. VMD provides the modeler with a large number of tools to, e.g., calculate the electrostatic potential or solvent accessible area. It also supplies an extensible and versatile scripting interface with which the user can create custom scripts tailored to individual needs.

VMD as a Database Access Tool

With the current explosion of biological data, publicly accessible databases are thriving and VMD intends to take full advantage of these resources. This is an excellent way to propel VMD into new areas and new user communities. Currently, VMD can retrieve atomic structures and density maps by their identifiers. The next level of integration will allow users to automatically query online databases based on the currently viewed structures. The results of these queries will be seamlessly incorporated into the visualization process. For example, VMD will be able to submit a protein's sequence to the leading databases (such as SwissProt) to perform sequence comparisons and alignments and, based on the result, will automatically display the protein's conserved regions. Similarly, all related structures (SCOP and PDB databases) or electron density maps (EDM database) can be automatically retrieved. Additionally, VMD allows the calculation and display of a wealth of physical properties such as energies, hydropathy indices, cavity maps, etc., as well as retrieving database-wide statistical averages (STING database). Each analysis will be at the scientist's fingertips and fully automated. Finally, a new tool is being designed which allows VMD to act as a data-mining engine to the entire PDB database using queries based on VMD's powerful atom selection functionality, allowing the scientist to count, retrieve and analyze all known structures containing a desired motif.

VMD's Unique Strengths and Use of Technology

VMD applies cutting-edge technologies to type task of rendering and analyzing biomolecular data, giving it unique capabilities not found in other software. VMD is the first molecular visualization program to use OpenGL Programmable Shading Language to render molecular graphics with ray traced geometry at interactive rates on a desktop computer, yielding shading quality previously attainable only with batch-mode molecular graphics software. Future development of programmable shading in VMD will move its "visualization kernel" onto the graphics accelerator, increasing performance and providing molecular graphics representations, which could previously be produced only by batch-mode rendering software. With support for a diversity of input and display modalities, VMD provides the visual, input, and haptic feedback components of interactive molecular dynamics simulations done with NAMD, Protomol, and other simulation engines. VMD is also unique in its strong support for interactive display and analysis of very large datasets, whether large structures, molecular dynamics trajectories, volumetric datasets, or loading thousands of molecular structures concurrently. With its use of

64-bit processors and efficient internal data structures, the dataset sizes supported by VMD are limited only by the memory capacity and processor speed of the host computer system and its graphics accelerators. Future VMD development will add further support for multi-core and multi-processor visualization systems, and automatic submission of long-running analysis and visualization batch jobs to GRID-based compute farms through BioCoRE.

2. NAMD

This is a "stellar" realization of the TCBG. In the last few years, NAMD has become **"the only"** computer program with the ability to simulate full atomistic models of large biological macromolecular systems efficiently on large parallel computers. The program uses state-of-the-art simulation algorithms and methods, well-validated atomic force fields (CHARMM and AMBER), and cutting-edge technology in parallel computing. The high success in NAMD is, to large extend, due to the professional computer science approach to load balancing, and the porting of the program to various architectures (including the new BG/L). Continuing efforts along these lines will bring molecular dynamics simulation to a stage were it can be used as a computational 'microscope' to view molecular processes at work.

During the last years NAMD has clearly caught up in terms of user numbers. In the computational community, NAMD is the most widely used molecular dynamics modeling program today. Of course, NAMD depends on the force fields of CHARMM and AMBER. Despite the fantastic progress, it is essential to understand that molecular dynamics (MD) still needs fundamental development that justifies funding at an NIH / NCRR Resource level. There are mainly five reasons.

First, there is an increased usage of MD modeling in experimental laboratories, e.g., to guide experimental studies by exploiting available structures or to take advantage of new structures for explanation of structure - function relationships. Second, the size of structurally resolved proteins and macromolecular assemblies is increasingly large, e.g., ATPase, proteasome, ribosome; the recently resolved structures can be studied effectively at the atomic level only with NAMD. Third, computational technologies have seen an increase of over 1000 in processor count x speed during the last ten years and promise another advance by a factor of more than 100 during the next five years through larger parallel computers and an increase in speed through co-processors. Few programs other than NAMD can take advantage of this opportunity (IBM develops a new MD program for its Blue Gene series of computers; D.E. Shaw and Co. are preparing a new MD code and computer for release in 2008 reaching supposedly ms simulation times); deploying the new generation of computers definitely will require major development and funding as the examples of IBM and D.E. Shaw and Co. shows. Fourth, interactive MD is, for the first time, promising to become an affordable methodology permitting the tinkering

with biomolecules on-the-fly, thereby, testing and developing hypotheses regarding protein function. Fifth, multi-scale modeling, considered key for linking atomic level with cellular level descriptions, requires major reprogramming of existing MD codes and force fields.

Accessibility to experimentalists

NAMD has always been targeted to a broad base of users interested in harnessing the power of parallel computations for their MD simulations. As such, the program is designed to be simple to use even by an inexperienced user, such as a student or a researcher with no extensive background in computer simulations, or a user of a different MD package. The current version of NAMD can be started with a script as simple as a few lines, filling the omitted simulation parameters with reasonable defaults. Using the interactive features of VMD, a simulation can be jump-started from a molecular viewing screen. The TCB group website provides an extensive user guide, detailed step-by-step tutorials, successfully taught at several workshops, and a number of easily adaptable sample simulations of systems of different sizes. The built-in PSFGEN utility solves many common problems in biomolecular structure construction, such as building missing atoms and residues, with a minimal user effort. The running program provides a very clear and specific output, making it easy for a user to monitor the simulation and to detect potential problems. The future development plans include further simplifying simulation setup and run, creating more tutorials for diverse biomolecular systems and building a searchable online database of ready to run sample simulations.

Interactive simulation

NAMD has the unique ability to perform Interactive Molecular Dynamics (IMD) simulations in which VMD is used to not only visualize a NAMD simulation running locally, or even on a remote cluster, in real-time as it is computed, but also to interact with it by applying real-time forces to individual atoms using a 3D haptic device with force feedback. The haptic interface will be extended from simple linear forces to include torques and internal degrees of freedom such as distances and torsions, and also the ability to add persistent steering forces. Atom coloring will be used to display interactions between the steered sets of atoms and their environment. Data transfers between NAMD and VMD will be made more efficient and simulation performance will be translated into an intuitive ratio between the inertial and environmental forces perceived by the user. The sensitivity of the haptic interface grows quadratically with speed of the simulation, making maximum performance essential for its adoption. The AutoIMD plug-in of VMD automatically constructs a small, fast-running IMD simulation based on a subset of a larger molecule. NAMD is tuned to provide maximum performance for these small systems, currently achieving a speed of 1ps simulated per second on an SGI Altix. This shared-memory platform should allow long-running batch jobs to be preempted by interactive simulations, as the local Resource clusters have for several years, to provide

on-demand access to IMD capabilities.

3. BioCoRE

BioCoRE is a framework environment for collaborative biomedical research, research management and training. BioCoRE is designed to assist the entire research process, from talking with collaborators to performing simulation and collecting data, to preparing papers and reports. Available functionalities include document sharing, setting up, submitting and running simulations on local and distant servers (such as at national computer centers), shared file system, sharing molecular views, note book, control panel for instant messaging and notifications, web site library, and more.

The BioCoRE team identified the increase of users as one of the future challenges for BioCoRE and the Resource presented key strategies for enhancing the user base through the development of new APIs that enable the creation of modeling environments, virtual organizations, extending grid computing capabilities, and database access. Specifically, BioCoRE will be integrated with VMD to serve VMD users in many new ways and thereby introducing them into the BioCoRE community. The Resource will develop "open" BioCoRE projects that utilize BioCoRE for web sites and open access data, thereby making BioCoRE use more beneficial. BioCoRE will provide basic technological underpinnings for other Resource efforts in the next funding period by making them easily accessible through BioCoRE. BioCoRE communication capabilities will be further developed. Grid Computing through BioCoRE will enable BioCoRE members with supercomputer time to enjoy a wide variety of computational resources through a simplified access to biomedical software running anywhere. The Resource plans to work with the National Centers to insure that BioCoRE interface remains compatible with rapidly advancing grid standards. Another strategy to enhance BioCoRE usefulness and appeal is to implement support within BioCoRE for 3rd party software packages, starting with the popular simulation package, AMBER. Organizing databases through BioCoRE is another new effort the Resource is considering, intending to offer varied tools, such as powerful search engines and visualization tools that allow the user efficient access to specific data. The development of a set of tutorials geared towards life science researchers and describing how they can use BioCoRE to organize their groups, their teaching, their collaborations, their conferences, and their computing is another means the Resource will use to support target users.

The BioCoRE effort consists of two major functional components: research-specific software tools, and general collaborative tools. The capabilities of BioCoRE are impressive and can possibly serve a very large community. The shared visualization has an immense potential, and the promised integration of 3rd party applications can make the environment highly relevant and useful. BioCoRE file system in particular has a tremendous possibility as a community tool. The common file system is an excellent way to share files during on-line discussions. Users can remotely exchange and discuss data. It would

be a substantial improvement if the data could be immediately visualized in the browser without all users having to have VMD installed on their local desktop. Furthermore, the common file system could be extremely useful as a prototype of a global filesystem for usage at the TeraGrid. Currently the TeraGrid does not provide a global filesystem and consequently data management is extremely painful. An externally provided user-initiated filesystem would be a significant improvement. The job submission for NAMD runs into the various TeraGrid queues is an admirable undertaking and enables researchers to manage the capabilities of the TeraGrid to a significantly better extent. In particular the job queue preparation, job monitoring, and data handling are of key importance for smooth and simplified operations on the TeraGrid. This is an example of a user community developing the software needed to fully utilize a National Resource fully. The more general tools such as discussion groups, message systems etc can be very useful for the creation and the vital support of a user community.

To proceed in a coherent manner and address further meaningful research needs, the BioCoRE team will have to define more clearly the user community it intends to support, identify their requirements, and populate the BioCoRE environment with functionalities addressing them. For example BioCoRE could become an indispensable platform for the data-driven bioinformatics community. The Resource may also want to consider folding the new proposed HBPS with its research-oriented features and workflow manager into BioCoRE. Treating the growing population of Resource workshop participants as potential BioCoRE members offers another means to increase the BioCoRE user base. A growing user community will enhance the overall impact of BioCoRE and will foster further and more fruitful collaborations across distances and locations.

4. HPBS

We are very excited about the development of the High Productivity Modeling Suite (HPBS). HPBS is a system for integrating VMD, NAMD (or other molecular simulation software), and BioCORE along with modeling modules. This tool will provide a comprehensive environment for physical modeling of biological systems. With this tool researchers will be able to perform novel simulations with less preparation time and a shorter learning curve. The HPBS will also serve as a tool to teach new researchers protocols commonly used in molecular modeling. The experienced user could use the HPBS as a way of generating scripts and for documenting how calculations were performed. .

The HPBS Builder module will allow a researcher to generate, in just a few minutes, a complete microscopic model of his/her biomolecular system, ready to be explored with computational engines. The model can either be built from scratch, or around a known molecular template, e.g., an X-ray structure, and can include proteins, nucleic acids, sugars, phospholipids, water, ions as well as coarse-grained objects. An automated procedure will configure the force field parameters and assign protonation and rotamer states. More

sophisticated steps could, in principle, be added to the protocols to perform pKa calculations, loop building, etc. For example, Bioinformatics tools included in VMD will provide the means to perform multiple structure alignments, multiple sequence alignments, generate phylogenies, query databases for structures with high sequence identity, and provide input to visualization tools in the form of residue and structure conservation metrics

The HPBS will provide a rich environment within which to perform simulation analysis tasks. It will support batch-oriented analysis workflows such as those commonly used with CHARMM, GROMACS, and AMBER, as well as interactive analysis tasks run within visualization tools like VMD, Matlab, and Mathematica. The HPBS will also implement a framework for standardized access to various computational engines which will perform the brute-force behind-the-scenes work. These computational engines will include existing simulation programs such as NAMD, AMBER, and GROMACS, and other tools such as electrostatics solvers and high-quality graphical renderers. With the increasing prevalence of grid infrastructure, it is becoming easier for these engines to access remote computational resources. The HPBS will connect with BioCoRE to implement a standardized interface to grid-based computational resources.

The HPBS will include tools that allow users to set up simulations of the dynamics of molecular systems. The Equilibrator Tool uses the computed force field to bring a system into a geometry thermodynamically attuned to its environment. The Simulator Tool simulates already equilibrated systems to sample fluctuations and relaxations in different ensembles. The Steering Tool applies external forces to biomolecular systems to probe their mechanical functions based on the SMD method. The Energy Tool allows for quantitative analysis in terms of energies associated with biomolecular manipulation, e.g. free energy difference or energy landscapes, based on the equilibrium and non-equilibrium thermodynamics (e.g., the Jarzynski identity). HPBS will make extensive use of visualization tools in VMD, and the collaborative tools in BioCore. One possible positive outcome of the HPBS tool would be to provide access to the complete history of the modeling process will allow complete simulation protocols to be easily reproduced, as well as abstracted and applied to new input data or molecular systems. These protocols could be distributed to the research community that evaluates the scientific work as well as to other researchers interested in reproducing the data.

5. Collaborations

The unique strength of the Resource resides in large scale simulations of biomolecular systems and the collaborations in the past funding period provided the collaborators with the Resources computational infrastructure and expertise in the field of molecular simulations. Most of the collaborations are within the US and are between the leading experimental groups in the field and the Resource. The Resource has completed an impressive number of 24 joint publications through these collaborations. Seven collab-

orative projects have been concluded during the last year. Currently the Resource is engaged in 22 different collaborations. Over the next year, the Resource will continue to closely work with research groups that need to complement their ongoing research with simulation methodologies or plan to integrate computational methods in their research. Planned collaborations include the simulation of ribosome, bacterial flagellum, and virus capsid maturation. Important for each of the collaborations is the biomedical relevance of the investigation, usually obvious from the fact that projects are NIH funded on the side of the collaborator, as well as relevance of the Resource methodology.

The Resource is and was engaged in excellent collaborative projects with mainly experimental laboratories. The focus continues to be on computational experimental collaborations that benefit from the methodological expertise as well as from their expertise in membrane systems and mechanical functions of cells. Excellent planned collaborations include cyro-EM based modeling of ribosomes and some truly forward-looking collaborations will comprise studies on bio-nano technology inspired projects.

Completed Collaborations

- Helix-helix interaction in membrane proteins - D. Engelman (Yale)
- Gold binding protein - M. Serikaya (Univ. Washington Seattle)
- DNA-protein interaction in Lac repressor - L. Mahedevan (Harvard)
- Rotary mechanism of Fo-ATPase - R. Fillingame (Madison)
- Mechanical properties of Fibronections and Integrins - V. Vogel (Washington U.)
- Holliday junction - T. Ha (UIUC)
- Selectivity and permeation in aquaporins - R. Stroud (UCSF)
- Proton transfer in bacteriorhodopsin - H. Kandori (Nagoya Inst. Tech.)
- Multiscale modeling of biomolecular systems - R. Phillips (Caltech)

Ongoing Collaborations

- Ion conduction of aquaporin-1 - A. Yool (U. Arizona)
- pH control of water permeation in aquaporins - J. Hall (UC Irvine)
- Ligand binding in nicotinic acetylcholine receptor - Cladio Grosman (UIUC)
- Nuclear pore complex - A. Sali (UCSF), M. Rout (Rockefeller), M. Stewart (MRC)

- Engineering hydrogenase - P. King/M. Siebert (NREL)
- Gas conduction in proteins - M. Sansom (Oxford)
- Nanodiscs - S. Sligar (UIUC)
- F1-ATPase - J. Weber (Texas Tech)
- Nanopore device for DNA sequencing - G. Timp / J. P. Leburton (UIUC)
- Mechanical stability of T4 lysozyme - C. Bustamante (UC Berkeley)
- Hemolysin - A. Meller (Harvard)
- Protein translocation through SecY - T. Rapoport (Harvard)
- Antrax - V. Vogel (ETH, Zurich)
- Titin - F. Wilmanns (Hamburg)
- Helicase - T. Ha (UIUC)
- Photosystem I in plants - P. Fromme (Arizona)
- GB1 Fibril - C. Rienstra (UIUC) and A. Gronenborn (NIH)
- Protein Folding - M. Gruebele (UIUC)
- Cadherin - D. Leckband (UIUC)
- Molecular basis of hearing - D. Corey (Harvard)
- Mechanosensistive channels - E. Perozo (Virginia)

Planned Collaborations

- STMV capsid - A. Mac Pherson (UCI) and J. Johnson (UCSD)
- Ribosome - J. Frank (HHMI, Wadsworth Center)
- Nanotubes - M. Strano (UIUC)
- Rotary Switch Mechanism of Flagellin - K. Namba (Osaka U.)
- 4pi Microscopy - R. Peters (Muenster U.)
- Time resolved investigation of PYP activation - K. Moffat (U. Chicago)

6. Training

The Resource uses training to help others do research and bring about discovery. The major training opportunities presented and planned are:

1. The Resources training efforts in the past year have been focused on holding hands-on workshops and participation has reached already about three hundred. The Resource offers participants presentations, written tutorials, personal Macintosh laptops, each acting as a complete package with all the necessary materials and software, and computer power for running practice jobs.

2. The Resource is planning to write an electronic and printed textbook compiling all the training material into a single book that will exist both in electronic and print versions, and will allow an investigator to conduct self-guided instruction on molecular modeling in a comprehensive way. The book will contain both the material and software required for learning, including lecture notes, tutorials and case studies, and will be updated regularly. There is a publisher the Resource is working with.

3. The Resource is about to embark on re-writing and extending the current tutorials to more platforms, expanding their distribution via the web and through CDs to complement the textbook.

4. The Resource will continue to offer training courses on computational biophysics. The Resource will also offer three workshops annually – an off-site workshop, an on-site workshop, and an on-line workshop. All workshops will take advantage of the BioCoRE environment for training, practice job runs and communication. Visiting collaborators and graduate students will also benefit from the Resources training capabilities. To complement its technical service the Resource will offer two courses annually on cluster computing, and will make them available online via streaming video, and for download.

5. The Resource will seek funding to support and facilitate the introduction of undergraduate students to computational biology in order to enhance current life science education.

The Resources training efforts are exceptional in breadth and depth. In the past two years the Resource experienced an explosive development in its training offering and the commitment to training, and the use of the latest technologies to enable training is exemplary. Using its limited resources in a cost-effective and intelligent manner it is impressive what the Resource has managed to accomplish. It would be interesting to include in the 2005 renewal proposal a section on trainees feedback and the impact of the

Resources training on their later work, use of computational tools, use of the Resources software packages.

7. Service

While in the past, the Service, Training, and Dissemination categories were combined into one area, now the Service section must stand on its own. The definition of Service normally used by the NIH primarily refers to "shared instrumentation", such as an electron microscope. While the Resource a local equivalent, namely its computational facility, this is currently primarily of use for internal users, and cannot be directly called a "service".

This challenge will be addressed in two directions. First, the Resource will continue to offer technical advice to both external users and users of the Resources major software packages, and will maintain the Resources seminar series. Second, the Resource will turn its visitor program into a full-fledged visitor center. By increasing the quantity of researchers utilizing the Resources technical facilities, and improving the quality of the environment that they work with, this will become a bona-fide service to the research community that could not be provided elsewhere.

During the past three years, 22 researchers from various universities and institutes across the world have visited the Resource, making use of its computational and visualization facilities while working closely with Resource members. Additionally, the Resource currently provides 65 remote users with full access to the Resource's computational facility, allowing researchers across the country to run simulations on its in-house cluster. In the course of the next year, the Resource envisions expanding the services provided to visiting researchers through a new visitor center. Among other enhance support capabilities, the visitor center, which will be housed alongside the Resources current office space beginning this year, will feature a suite of desktop visualization machines for individual study, as well as a seminar room for collaborative work and presentations and other. By establishing this visitor center, the Resource will be able to share its technological resources (described below) with an increasing number of external researchers.

The Resources efforts and record in the Service area are extraordinary and their use of their limited resources for this purpose, generously sharing their expertise with the larger community, is exceptional. The use of in-house databases to track use of resources and monitor services is remarkable and provides them with regular snapshots of their operational accomplishments and challenges, as well as the best data for long- and short-term planning, for reporting purposes, for dissemination and outreach, and more.

The Advisory Board is highly supportive of the new plan to open a Visitor Center. However to make the new Visitor Center a reality a new space allocation is urgently needed in order to offer the visitors a reasonable work environment. The Visitor Center

stands to benefit the Resource, Beckman and the University and the Advisory Board urges the Beckman Director in the strongest possible terms to assign the required area to the Resource on a long-term basis.

8. Dissemination

Communicating technological and research efforts to the biomedical community requires that the Resource actively utilizes a variety of traditional and internet-based channels. Over the past year dissemination activities included 34 publications in refereed journals, 60 talks, outreach activities such as special lectures series, responding to image requests, and licensing. The Resource has also been covered by various external media agencies.

Importantly, the tool with the widest outreach to the scientific community is the Resource website, with approximately 423,000 visitors, 985 gigabytes of downloads, and nearly 1,000 links to the home page over the past year. Maintaining this level of website success requires that the Resource engage in an ongoing process of revision, update, and exploration of what the website can provide to the biomedical community. Planned improvements include addition of various features to the software application websites, and revised, reorganized and updated research and training pages. Furthermore, new pages will be created, devoted to description of prior and current collaborations, and to summarizing news from and about the Resource. The Resource is also working with professional website designers to develop a new 'look' for the Resource website.

The dissemination component is exemplary and captures the entire range of the Resources efforts, delivering accomplishments to the wider community in an effective, friendly and timely manner. The plans to overhaul the web page are outstanding, and the new sections promise to be very useful. Identifying and cross linking collaborative projects on the new planned web section to those Resource software technology pages that supported the specific research will be useful, and would also serve as a tracking mechanism for reporting purposes, demonstrating the mutual benefits to both the collaborative project and the Resources software in question.

For future growth it may be useful to consider content management systems (CMS) that are fully database driven, rather than an accumulation of individual web pages. There are open source community portals available such as MAMBO for such purposes. This will enable a distributed content management system, where a variety of contributors can provide content in a web-based environment.

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