DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

NATIONAL CENTER FOR RESEARCH RESOURCES
BIOMEDICAL TECHNOLOGY AREA

ANNUAL PROGRESS REPORT (8/1/97-7/31/98)

NIH RESOURCE FOR MACROMOLECULAR MODELING & BIOINFORMATICS

1. PHS GRANT NUMBER: P41RR05969

2. NAME OF RECIPIENT INSTITUTION: Concurrent Biological Computing

3. HEALTH PROFESSIONAL SCHOOL (If applicable):

4. REPORTING PERIOD:

A. FROM (Month, Day, Year): August 1, 1997

B. TO (Month, Day, Year): July 31, 1998

5. PRINCIPAL INVESTIGATOR:

A. NAME: Klaus J. Schulten

B. TITLE: Professor

C. SIGNATURE:

6. DATE SIGNED (Month, Day, Year):

7. TELEPHONE NUMBER (Include Area Code): (217) 244-2212

8. FACSIMILE NUMBER (Include Area Code): (217) 244-6078

9. ELECTRONIC MAIL ADDRESS: kschulte@ks.uiuc.edu

10. Was Patent of Copyright awarded this grant year: N

11. Total % effort related to AIDS research: 0%

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Contents

This report describes research, development and service activities in 1997-98 at the National Institutes of Health funded Resource for Macromolecular Modeling and Bioinformatics. The report covers the 8th funded year of the Resource. This is the first year of a new five-year funding cycle awarded to the Resource. As reflected by its new name and indicated in the renewal proposal, the Resource has redefined itself and modified its mission. Accordingly, the report emphasized rebuilding efforts over accomplishments, and ongoing and young projects over completed ones.

The Resource development efforts, aimed at fully utilizing high performance computing in studying molecular biology of cells, have benefited many collaborative projects and have provided a conceptual framework to fight diseases. During the past year our efforts have been directed at:

- Integrating Prof. T. J. Martínez' quantum chemistry methods.
- Formulating theoretical concepts applicable to large aggregates.
- Developing software to model and view ever-larger biomolecular units.
- Exploring cost effective computer platforms and maintaining a state-of-the-art computational laboratory.
- Broadening the scope of our software development to include network-based collaborative tools.
- Bridging a gap between laboratories where large biomolecular structures are discovered and measured, and computational laboratories where the expertise for very large scale molecular modeling resides.
- Engaging in demanding and relevant collaborations.
- Initiating service, training and dissemination activities.

The quantum chemistry research of a new Co-PI Todd Martínez has proven well timed and successful. Improved structural information and extended research agendas in molecular cell biology as well as rapid conceptual advances signal the onset of a new generation of quantum simulation methods. Resource researchers, in applying methods developed by Martínez and employing the Resource simulation program NAMD, have carried out a landmark full quantum mechanical simulation of the 2 ps photoprocess in bacteriorhodopsin (bR). The simulations revealed how the geometry of the binding site of the chromophore retinal in bR, together with the characteristics of retinal's electronic potential surfaces, can steer the photodynamics of retinal towards the reaction product that triggers proton pumping. As part of its effort to improve the quality of potential energy surfaces used in molecular dynamics simulations the Resource, under the leadership of Martínez, is also examining hybrid quantum/classical methods.

Software and method development for very large biomolecular systems is a key goal of the Resource. The MDScope package developed by the Resource has been enhanced with new versions of its two basic components, the visualization program, VMD and the parallel molecular dynamics program NAMD.

A new beta version of VMD1.2 was released on May 12, 1998 and a release of the full production version is scheduled at the end of June 1998. VMD provides, more than ever before, a powerful base for implementing new methods in structure visualization and analysis. The number of VMD users has constantly increased over the past year and the program is gaining wider popularity and recognition.

The latest version of NAMD, NAMD2, is currently in local beta release and we anticipate a public release shortly. NAMD2 is closer than previous releases to realizing the NAMD design goals of modifiability (including a TCL-based scripting interface), speed, and of parallel performance on a wide variety of parallel computers. The new structure of the program exhibits improved sequential speed and better parallel performance on machines with dozens to hundreds of processors, resulting in an order of magnitude increase in the speed of the simulations. Work on algorithm development has demonstrated the viability of new time-stepping schemes that push the length of the time-step beyond the 5 fs barrier that limits the best current schemes.

In the past year the Resource's computational facility has been upgraded in order to further meet our increasing computational and visualization needs. We have expanded our graphics and computing power and capabilities with the addition of several systems, the most significant one being an SGI Onyx2 InfiniteReality Rack with eight 195 Mhz R10000 parallel processors sharing one gigabyte of RAM.

Joint studies with experimental groups are a principal mission of the Resource and constitute a measure of our success. Such studies have concentrated on large systems and long time scale simulations that would have been impossible without the advanced computational methods, hardware, and expertise available in the Resource. Projects include modeling of protein-membrane complexes, modeling regulation and packing of DNA by proteins, and exploring structure and function relationship of bioenergetic proteins.

A sample project in large structure modeling focused on apolipoprotein A-I (apoA-I), the primary protein constituent of High Density Lipoprotein (HDL) which circulates in the bloodstream, extracting cholesterol from body tissues and transporting it to the liver for excretion or recycling. Another example builds on the Resource's expertise in combining large structure modeling, crystallography and electron microscopy and attempts presently to solve the structure of aquaporin-1 (AQP1). AQP1 is an extremely abundant protein in the body, which acts as a highly selective water channel in, e.g., the kidney. Further examples are simulations of proteins involved in the regulation and packing of DNA. Resource researchers have studied the interaction of DNA with lac-repressor, DNA hydration patterns influencing sequence specific DNA protein interactions and hormone, e.g. estrogen, binding to a nuclear hormone receptor protein. The collaborators in the latter investigations include L. Mahadevan of MIT for the *lac* repressor, and biochemists J. Katzenellenbogen and R. Gumport of UIUC for hormone receptors and DNA hydration. Mechanical proteins are the subject of ongoing collaborations with biophysicists V. Vogel of University of Washington, Seattle and J. Fernandez of Mayo Clinic, Rochester. These proteins provide elastic frameworks for tissues such as muscle (titin), cell adhesion (cadherin, fibronectin and integrin), and neural development (NCAM). The protein cadherin is implicated in certain types of cancer. Individual proteins can be stretched by atomic force microscopy, and a new simulation method developed at the Resource, steered molecular dynamics, permits one to interpret these experiments in atomic detail. Steered Molecular Dynamics (SMD) simulations have also been applied to other biomedically relevant proteins such as nuclear hormone receptors (see above) and examples mentioned further below.

The Resource has served the community of biomedical researchers at UIUC as well as elsewhere, through its software, facilities, collaborations and training efforts.

The Resource offers technological services, designed to provide the scientific community with easy access to the Resource's software and hardware technology and general services which focus on creating new collaborations, sharing the knowledge and expertise produced by existing collaborations, and ongoing application projects with other biomedical scientists. The 3-D projection facility of the Resource is often utilized by researchers and students from Illinois, and by visitors to the Resource. A seminar series run by the Resource brought over 26 renowned researchers to the campus community. The Resource distributes its software package MDScope, with the programs NAMD and VMD; via the World Wide Web. Since June 1, 1997 NAMD has been downloaded 840 times and VMD 1,700 times. A new VMD CD has been produced and will be distributed to interested users.

The Resource continues to fully benefit from the wide array of communication and dissemination tools available today. All software manuals and documentation are posted on our web site, as well as images and results of recent work (*http://www.ks.uiuc.edu/*); research and development accomplishments are published in professional journals and are posted on the web; lectures and talks describing the Resource activities are given all over the world; various documents such as reports and brochures, are periodically mailed to colleagues, prospective members, and federal offices, and are posted on the web (*http://www.ks.uiuc.edu/Publications/*). A search of the web indicates that there are over 500 links to our web pages and it is highly visited. The staff continuously reports key findings and systematically disseminates new knowledge produced by the Resource.

As in previous years the training activities at the Resource greatly overlap with the service and dissemination efforts. Additionally, the Resource's Principal Investigators advise postdoctoral fellows, graduate students in their respective departments and offer rotation opportunities to undergraduates. In the past year the Resource hired four new postdoctoral researchers, a new graphics programmer and a new system analyst.

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Steered Molecular Dynamics

Molecular recognition and specific ligand-receptor interactions are central to many biochemical processes. The regulation of cellular signal-transduction pathways and gene expression, activity of enzymes, cell motility, molecular immunology and the action of hormones involve the triggering of functional responses by noncovalent associations of ligands with receptors. Despite an abundance of modeling methods for ligand-receptor interactions and protein-protein docking [1, 2], little is known about processes governed by adhesive interactions such as those occurring in the binding and unbinding of ligands.

In Steered Molecular Dynamics (SMD) simulations[*], time-dependent external forces are applied to molecules – for example to a ligand, to facilitate its unbinding from a protein. The analysis of the interactions of the dissociating ligand with the binding pocket, as well as the recording (as a function of time) of applied forces and ligand position, yields important information about the structure-function relationships of the ligand-receptor complex, binding pathways, and mechanisms underlying the selectivity of enzymes [3-7]. SMD can also be applied to investigate the molecular mechanisms that determine elastic properties exhibited by proteins subject to deformations in Atomic Force Microscopy (AFM) and optical tweezer experiments [7].

Besides producing qualitative information, these biologically and pharmaceutically driven applications of SMD can also yield quantitative information about the binding potential of the ligand-receptor complex. A first step in the reconstruction of the thermodynamic potential from SMD data by discounting irreversible work was made by Balsera, et al. [8].

Avidin-Biotin (7,800 atoms)

The avidin-biotin complex, known for its extremely high affinity, has been studied experimentally more extensively than most other protein-ligand systems [9-11]. SMD simulations were performed on the entire tetramer of avidin with four biotins bound to investigate the microscopic details of unbinding of biotin from avidin [3].

Contacts of biotin with nonpolar residues, especially with Trp110 of an adjacent avidin monomer (in the complete tetramer), are crucial for the unbinding process. These residues prevent water molecules from entering the binding pocket. To determine the effect of water molecules on the unbinding mechanism, water molecules were placed in the avidin tetramer with the program DOWSER [12]. The presence of four water molecules in the outer region of the binding pocket, reduced the rupture (maximum) force as shown in Figure 1. The reduction of the rupture force resulted from the participation of water molecules in breaking the hydrogen bond networks between biotin and residues located near the exit of the binding pocket. Water did not penetrate the binding pocket on the time scale of the simulations.

[*] *URL: http://www.ks.uiuc.edu/Research/METHOD/force_pull/*

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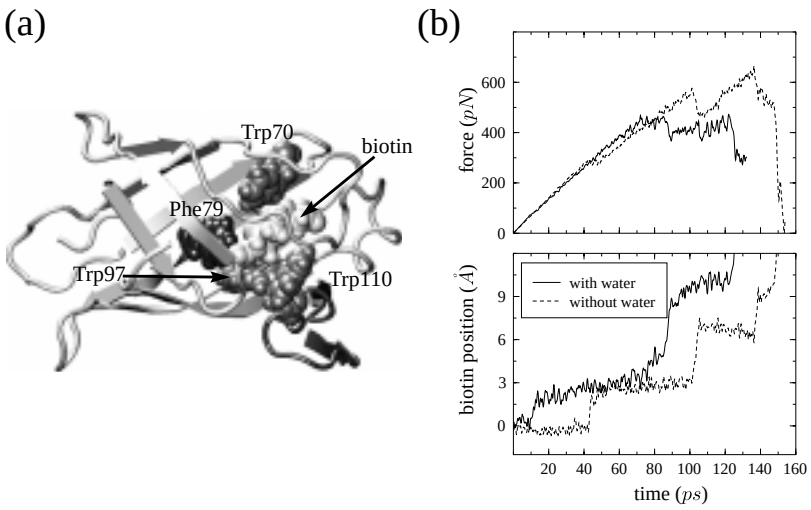

Figure 1: (a) Hydrophobic residues in the binding pocket of the avidin-biotin tetrameric complex (only one monomer shown): Phe79, Trp70, and Trp97, as well as Trp110 from the adjacent monomer, surround biotin tightly on all sides making the binding pocket impenetrable to water. (b) Biotin displacement and applied forces during the dissociation of the avidin-biotin complex with and without water molecules in the vicinity of the binding pocket. This figure was created with VMD [13].

Extraction of Lipids from Membranes (16,000 atoms)

Lipids are extracted from membranes by various enzymes. One such enzyme is phospholipase A2 (PLA2), which complexes with membrane surfaces, destabilizes a phospholipid, extracts it from the membrane, and catalyzes the hydrolysis reaction of the *sn*-2-acyl chain of the lipid, producing lysophospholipids and fatty acids [14-16]. SMD simulations were employed to investigate the extraction of a lipid molecule from a DLPE monolayer by human synovial PLA2 (see Figure 2b), and to compare this process to the extraction of a lipid from a lipid monolayer into the aqueous phase [5].

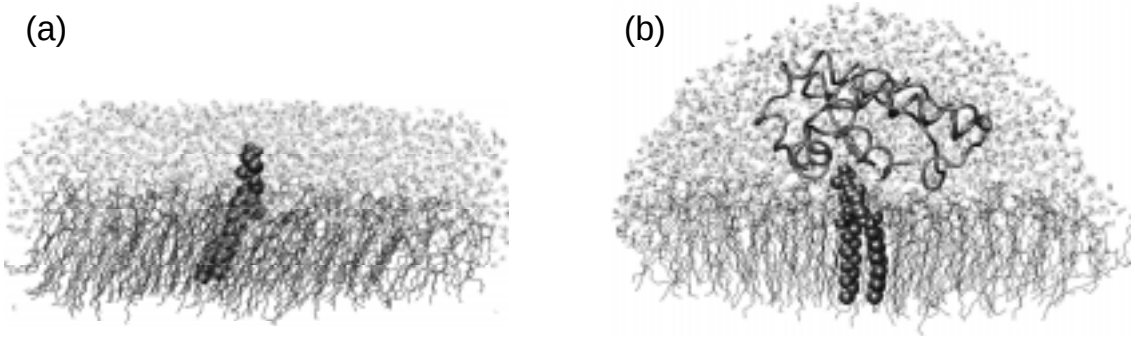

Figure 2: (a) Extraction of a lipid (black spheres) from the DLPE monolayer (lines) into the aqueous phase. (b) Extraction of a lipid (black spheres) from the DLPE monolayer (lines) into protein phospholipase A2 (tube) solvated in water. This figure was created with VMD [13].

Binding Pathway of Arachidonic Acid in Prostaglandin H_2 synthase-1 (9,000 atoms)

The enzyme prostaglandin H_2 synthase-1 (PGHS-1) catalyzes the transformation of the essential fatty acid, arachidonic acid (AA), to prostaglandin H_2 [17]. Based on the crystal structure of

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PGHS-1, with flurbiprofen bound at the active site, a model for AA embedded in the enzyme has been suggested, in which AA replaces the inhibitor [18]. SMD calculations on a monomeric PGHS-1 (see Figure 3) were carried out leading to the enforced unbinding of the ligand from its narrow hydrophobic binding channel. The type of concerted motion observed during unbinding is specific for the chemical structure of AA and is important for the binding and recognition mechanism.

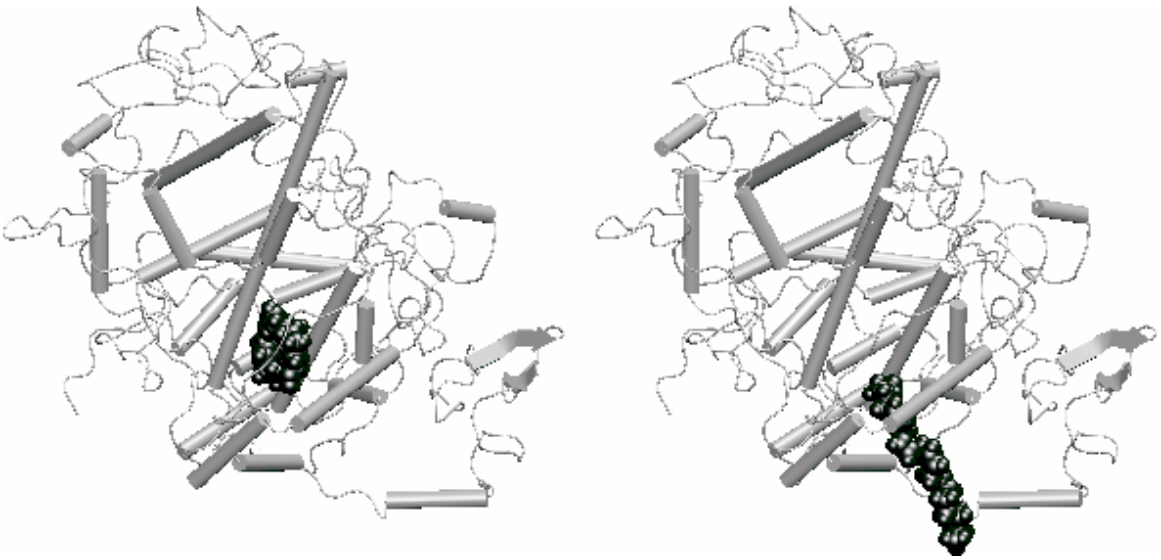

Figure 3: Unbinding of arachidonic acid (black spheres) from the cyclooxygenase active site of prostaglandin H_2 synthase-1 (gray cartoon). This figure was created with VMD [13].

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The Parallel Molecular Dynamics Program NAMD

NAMD [19] is the parallel molecular dynamics simulation component of the MDScope computational environment. It can be used alone to perform molecular dynamics (MD) simulations, or along with VMD [13], the visualization component of MDScope, to interactively view and manipulate running simulations. NAMD1.3 was released in 1995. The latest version, NAMD2, is currently in local beta release, and we anticipate a public release shortly.

One of the main design goals of NAMD2 was to allow easier code modification. The improved modifiability has allowed us to add a number of features to NAMD2 which were not part of previous NAMD releases. NAMD2 now supports periodic boundary conditions, using either cutoff electrostatics or full Ewald electrostatics. We have also implemented a triple time-stepping algorithm, doubling the short-range nonbonded time-step length. A prototype TCL-based scripting interface introduced in NAMD2 permits users to add new varieties of force calculations to their simulations. We plan to extend the script interface to allow user control of most of the simulation algorithm. NAMD2 includes support for all the features of NAMD1, such as full electrostatics simulation using the DPMTA library [20] from Duke University. NAMD2 includes the DPME electrostatics algorithm, developed also by our collaborators at Duke. In addition, users have modified NAMD2 to perform Steered Molecular Dynamics simulations (see SMD highlight).

	Processors			
Program	1	2	4	8
NAMD1.5	9.1	5.3	3.8	2.1
NAMD2	6.1	3.5	2.2	1.4

Table 1: Time per simulation step for a 15,000 atom simulation with an 8.5Å cutoff. NAMD2 is not using triple-time stepping (HP 735/125).

NAMD2 is designed to offer efficient operation on a wide variety of parallel computers. It is implemented on top of the Converse runtime system* [21], for easy porting to many parallel machines. NAMD2 runs on clusters of HP, Sun, and SGI workstations, as well as Linux machines using the KCC compiler. It also runs on the SGI Origin 200 and Origin 2000, the IBM SP3, the Convex Exemplar, and the Cray T3E. Sequential performance is better than NAMD1.5 (see Table 1). NAMD2 uses a hybrid parallel decomposition scheme, combining benefits of both spatial and force decomposition to achieve good parallel performance. NAMD divides the simulation space into cubical regions (patches), which are distributed among the processors. For NAMD1, distribution of these patches was the only means of load balancing. Since typical simulations only contain a few hundred patches, there are not enough pieces of work to balance the load across hundreds of processors. Spatial decomposition results in good communication efficiency, since patches need to pass atom coordinates only to their nearest neighbor patches. NAMD2 retains the patch decomposition scheme, but adds force computation objects (compute objects). Each pair of neighboring patches produces a compute object responsible for calculating

* *URL: http://charm.cs.uiuc.edu/*

the electrostatic forces between all pairs of atoms in those two patches. This results in 27 times more objects to be load balanced, allowing superior parallel performance. To ensure accurate load balance, we implemented an object-based load-balancing strategy [22] that migrates compute objects dynamically. Each compute object is instrumented by the system to measure the time spent in it. The load due to all non-migratable objects is also automatically measured. At periodic intervals, the timing data from all processors is collected. An analysis module constructs a communication graph, and finds an improved assignment of compute objects to processors. Compute objects are migrated to their new processors, and all the parallel data structures are updated accordingly. By employing actual load statistics (rather than estimates), and heuristic work assignment schemes, we were able to obtain significant performance improvements.

As a result of this extensive load balancing , NAMD2 has demonstrated good speedups for up to 128 processors on the Cray T3E (see Figure 4). Local users are taking advantage of NAMD2's parallel performance through production runs on as many as 64 processors*.

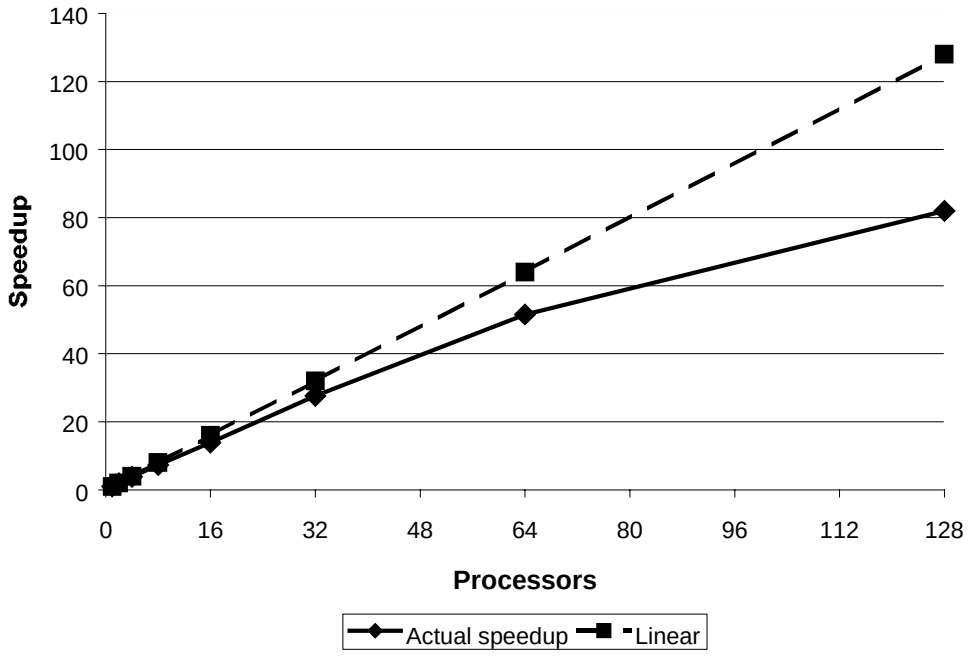

Figure 4: Speedup for NAMD2 running on a 37,000 atom simulation using a 12Å cutoff (Cray T3E).

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

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Elastic Rod Model of Lactose Operon DNA

Lactose operon repressor (*lac* repressor) is a protein that regulates lactose consumption by *E.coli* bacteria [23]. At the dawn of molecular biology, it was the study of this protein that inspired the concept of protein synthesis control via repression of gene transcription [24]. The *lac* repressor binds DNA in the absence of lactose, and prevents RNA polymerase from beginning the transcription. Thus, the cell does not produce the proteins responsible for lactose digestion when there is no need for them.

Lac repressor functions as a tetramer. Two pairs of sub-units bind two out of three DNA sites recognized by the protein. The binding induces looping of the DNA connecting the binding sites. In 1996, the crystal structure of the *lac* repressor-DNA complex was reported [25]. The protein tetramer was binding two synthetic DNA segments, emulating the natural binding sites. However, those were disjoint segments not connected with an intermediate DNA. Such an intermediate DNA segment would introduce a certain stress that would possibly alter the complex structure. We used the crystal structure to fill the gap, predicted the shape of the connecting DNA loop, and estimated the resulting stress.

Following previous work on elastic rod models of DNA [26-28], we approximated the DNA in the loop by an inextensible elastic rod[*]. The elastic rod model describes the DNA in terms of its center-line contour, the curvatures in two principal directions of the DNA cross-section, and the twist around the helical axis. The parameters of the model are two DNA bending moduli, which can be estimated from experimental data [29]. The theory of elasticity [30] results in a 13*th* order Kirchhoff system of differential equations, which completely describes the elastic rod. The crystal structure [25] provides boundary conditions for the problem, and a continuation method [31] was used to solve the resulting boundary value problem numerically. The method is based on a series of gradual changes in the elastic moduli and boundary conditions, from the values corresponding to a known solution to the desired ones. We started with a known solution for a relaxed closed circular rod with an isotropic cross-section [31] and accomplished the continuation procedure in three steps. In the first step, the DNA termini was translated to the desired distance. The termini acquired the proper orientation in the second step, and in the last step the anisotropy of the cross-section was turned on and the elastic moduli were gradually changed to their desired values.

Two possible configurations of the DNA loop resulted from our modeling, depending on the number of times a loop terminus was rotated at the second step of the iteration procedure. The solution with smaller energy exhibited also axial symmetry. This solution was recognized as a likely global minimum of the potential energy among the possible DNA conformations. The DNA loop corresponding to this solution is confined to a plane perpendicular to the roughly planar *lac* repressor-DNA complex, Figure 5. This DNA configuration does not agree with earlier expectations [25]. However, this DNA geometry may be energetically favorable since it allows a reduction in the electrostatic self-repulsion of the DNA. The estimated value of the DNA elastic energy is 15 kcal/mol, which is comparable to the observed energy of the *lac* repressor-DNA interaction [25]. The estimated value of the tensile force, -0.3 pN, is much lower than the force required to introduce significant conformational changes in the DNA [32, 33]. The

[*] *URL:http://www.ks.uiuc.edu/Research/pro_DNA/elastic/*

estimated low values of the bending energy and the tensile force suggest that the influence of the connecting DNA on the protein is small and the crystal structure of the *lac* repressor-DNA complex is close to the *in vivo* structure, when the protein binds continuous DNA. Our model assumes that the elastic parameters of the DNA correspond to those of the unperturbed structure, and the estimated low stress affirms this.

Higher resolution modeling can be used to explore the vicinity of DNA conformations obtained from the elasticity theory. We used the symmetric solution for the *lac* repressor-bound DNA loop to build an all-atom model of the DNA, which was subsequently minimized. We intend to explore the stability and properties of the structure in molecular dynamics simulations.

The set of Kirchhoff equations that we employed can be readily modified to provide a more detailed description of DNA. We derived the equations in a form that takes into account possible non-zero intrinsic curvatures of DNA sequences. Other effects that may be included in the models are the electrostatic interactions, and the dependence of the elastic parameters on the local DNA sequence. We plan to derive these equations and apply the modified Kirchhoff method to the study of other protein-DNA complexes, e.g., DNA wrapped around a nucleosome.

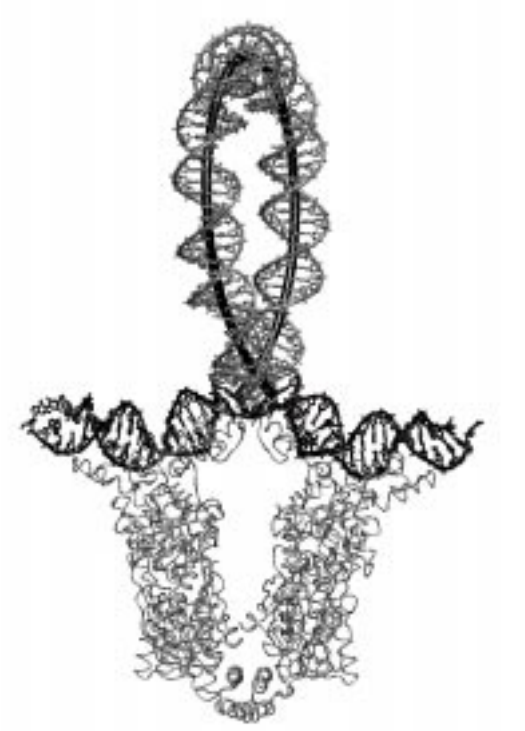

Figure 5: All-atom DNA fit on the contour predicted by the elastic rod model. The crystal structure of the *lac* repressor is shown in ribbons. The tube indicates the predicted elastic contour. This figure was created with VMD [13].

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Quantum Dynamics of Retinal's Femtosecond Photoisomerization in Bacteriorhodopsin

Bacteriorhodopsin (bR) is a protein that realizes the simplest known form of biological photosynthetic energy storage, absorbing light and converting its energy into a proton gradient across the cellular membrane of archaebacteria through vectorial proton translocation [34]. As its name indicates, bacteriorhodopsin is closely related to rhodopsin, the protein which acts as the primary light detector in the visual pathway of higher life forms [35-39].

In order to understand how proton transport is coupled to light absorption one must focus on the photodynamics of the retinal chromophore that intercepts the proton conduction pathway. Upon absorption of light, retinal undergoes a sub-picosecond all-*trans* $\rightarrow$ 13-*cis* phototransformation involving torsion around a double bond. The main reaction product triggers later events in the protein that induce pumping of a proton from the cytoplasmic side to the extracellular side. The arrangement of bR, as shown in Figure 6, is consistent with this pump mechanism.

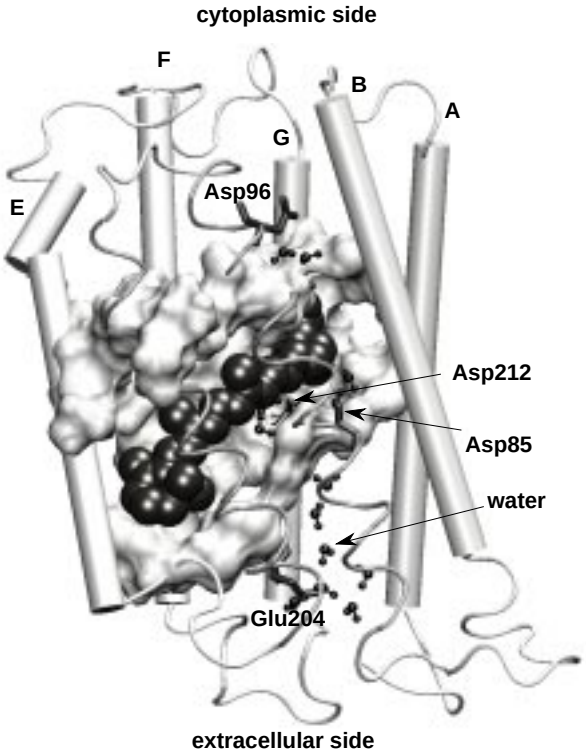

Figure 6: Bacteriorhodopsin and retinal binding site. Retinal is shown in van der Waals sphere representation, and part of the nearby residues are shown in surface representation. Transmembrane helices A, B, E, F, G are shown as cylinders, and helices C, D are shown as thin tubes to reveal the retinal binding site. For clarity, the rendering of the retinal does not show hydrogen atoms; as a result retinal appears less voluminous than in reality. This figure was created with VMD [13].

Since the primary phototransformation of bR proceeds on three coupled electronic states it cannot be described via a straightforward solution of Newton's equations of motion. Instead, the quantum mechanical nature of the nuclear degrees of freedom must be confronted. To this end,

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we have applied a formally exact quantum mechanical procedure, the full multiple spawning method for molecular dynamics on multiple electronic states [40, 41]. In this first application of quantum dynamics to protein photocycles a rich set of isomerization scenarios arose with compelling suggestions regarding bR's function*.

In agreement with previous classical [39] and combined classical/quantum mechanical molecular dynamics studies [42], we found a sub-picosecond time scale for the key primary processes– torsion around retinal's C_{13}=C_{14} bond and non-adiabatic crossings. The calculations predicted a photoisomerization quantum yield of 0.48 which is in reasonable accord with the experimentally observed quantum yield of 0.64±4 [43, 44]. The simulations also revealed the occurrence of two types of photoisomerization products. These had been previously identified with a putative precursor for the pump process and with a side product that could be of possible functional significance, e.g., in case of an overcharged bacterial membrane [39, 45].

Most intriguing in regard to functional implications is the observation that photoisomerization occurs in two opposite rotational senses and that the direction of rotation is correlated with the formation of different photoproducts. It appears that one rotational sense leads predominantly to a product which is likely to trigger proton pumping whereas the other rotational sense leads to a product which has been implicated with a reversal of proton pumping as it arises in certain mutants and possibly in the presence of electric fields under intense radiation [45, 46].

The present investigation will be considerably extended in the future. Foremost is a need to improve the potential surfaces of retinal. In particular, we plan to include the effect of electronic excitation on other degrees of freedom, thereby allowing for a conical-intersection. This could have a profound effect on the photodynamics since internal conversion is known to be extremely efficient when conical intersections are encountered. Another improvement that is needed is the recognition of the differing charge distributions and polarizabilities of the electronic states. This may be especially important in light of the importance of nearby ionized residues as elucidated by mutagenesis studies. A second great opportunity for a further advance arises through the availability of much improved structures of bR [47, 48].

* *URL:http://www.ks.uiuc.edu/Research/METHOD/quant_sim/*

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Force-Induced Unfolding of Titin Immunoglobulin Domains

The giant muscle protein titin, also known as connectin, is a roughly 30,000 amino acid long filament which plays a number of important roles in muscle contraction and elasticity [49-51]. Titin has been connected with the myasthenia gravis [52] and hypertrophic cardiomyopathy [53] diseases. The I-band region of titin, largely composed of immunoglobulin-like (Ig) domains, is believed to be responsible for the molecule's extensibility and passive elasticity. Recently, AFM [54] and optical tweezer [55, 56] experiments directly measured the force-extension profile of single titin molecules. In the AFM experiment, cloned sections of titin composed of adjacent I-band Ig domains were stretched at constant speed. The force-extension profile showed a sawtooth-shaped pattern with about 250 to 280Å spacing between the force peaks, with every force peak corresponding to a single Ig domain unfolding. The Ig domains were thus observed to unfold one by one, as opposed to concurrently, under the influence of applied external force. To examine in atomic detail the dynamics and structure-function relationships of this behavior, SMD simulations of force-induced titin Ig domain unfolding were performed [7].

The SMD simulations* were performed with an NMR structure of the Ig domain I27 of the cardiac titin I-band [57]. I27 consists of two β-sheets packed against each other, with each sheet containing four strands, as shown in Figure 7b. The domain was solvated and equilibrated, then an SMD simulation was carried out by fixing one terminus of the domain and applying a force to the other in the direction from the fixed terminus to the other one. Simulations were performed following the scheme of $F = K (vt - x)$ with applied force F, extension x, time t, $v = 0.5$ Å/ps and $K = 10\ k_BT/Å^2$ at 300K. The recorded force-extension profile from the SMD trajectory, Figure 7a, showed a single force peak at the initial stage of the Ig domain extension. This feature agrees well with the sawtooth-shaped force profile exhibited in the AFM experiment.

Examination of the details of the simulation trajectory explains the early force maximum (see Figure 7b). Initially (0–10Å extension), the two β-sheets slid away from each other, maintaining a stable structure as well as their intra-sheet backbone hydrogen bonds. As the extension of the domain reaches 14Å, the structure within each sheet begins to break: in one sheet, strands A' and G slide past each other, while in the other sheet, strands A and B slide past each other. The A'-G and A-B hydrogen bonds broke nearly simultaneously, producing the large initial force peak seen in Figure 7a. These events marked the beginning of the Ig domain unraveling, after which the domain gradually unfolded and strands unraveled one at a time, accompanied by a large reduction in the recorded force. After an extension of 260Å, the domains were completely unfolded; further extension stretched the already extended polypeptide chain and caused the force to dramatically increase.

The simulation suggests how Ig domains achieve their chief design requirement of bursting one by one when subjected to external forces. At small extensions, the hydrogen bonds between strands A and B and between strands A' and G prevent significant extension of a domain, i.e., the domain maintains its β-sandwich structure. After these bonds break, resistance to unfolding becomes much smaller, and the domain unfolds rapidly. Only when a domain is fully extended does the force increase enough to begin the unfolding process in another domain.

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

Grant Number: P41RR05969
Report PD: (8/01/97-7/31/98)

In future work, SMD simulations will be performed on assemblies of two and three Ig domains, in order to clearly observe one by one unfolding, and to observe the changes induced on a folded domain while a neighboring domain unfolds. We will also examine unfolding in other systems, such as fibronectin and cadherin, that, like titin, contain tandem β-sandwich domains and are subject to external force during normal function.

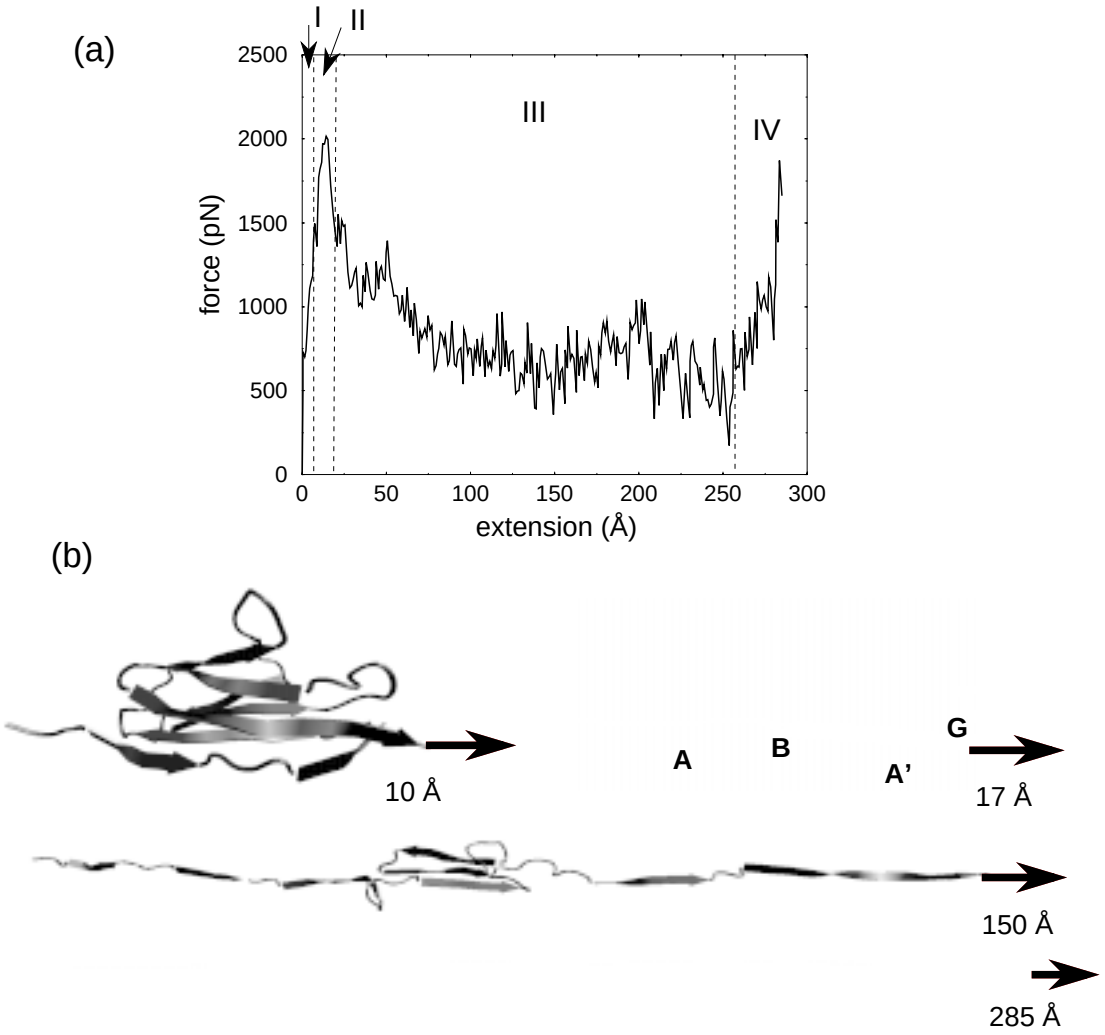

Figure 7: (a) Force extension profile of SMD simulations for I27 with a pulling velocity v = 0.5 Å/ps. The extension domain is divided into four sections: I. pre-burst, II. major burst, III. post-burst, IV. pulling of fully extended chain. (b) Intermediate stages of the pulling simulations. The I27 domain is drawn with cartoon representation; solvating water molecules are not shown. The four figures at extensions 10Å, 17Å, 150Å, and 285Å correspond respectively to regions I to IV defined in (a). This figure was created with VMD [13].

BTA UNIT: T, D

TITLE: Molecular Modeling: The Program NAMD

KEYWORDS: molecular simulation, modeling, parallel computation, object-oriented programming, message-driven programming

Axis I: 9

Axis II: 42, 84

INVEST1: Milind Bhandarkar

DEGREE1: M.S.

DEPT1: Department of Computer Science

NONHOST1:

INVEST2: Robert Brunner

DEGREE2: B.S.

DEPT2: Department of Electrical and Computer Engineering

NONHOST2:

INVEST3: Jim Phillips

DEGREE3: M.S.

DEPT3: Department of Computer Science

NONHOST3:

INVEST4: Krishnan Varadarajan

DEGREE4: B.S.

DEPT4: Department of Computer Science

NONHOST4:

% BRTP $: 20%

ABSTRACT: The simulation component of the MDScope modeling environment, NAMD [19], continues to undergo improvement in both features and speed*. The

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

latest version, NAMD2 (a complete rewrite of much of the NAMD code), is nearing a public release. NAMD2 goes further than any previous release in achieving the NAMD design goals of modifiability, speed, and parallel performance.

NAMD2 is more modifiable than the original version, as demonstrated by the features added in the last year. The program now supports periodic boundary conditions, using either cutoff electrostatics or full Ewald electrostatics. It allows larger simulation steps using a triple-time-stepping scheme, which can allow some simulations to run at double the speed of the original method. NAMD2 has a prototype TCL-based scripting interface that permits users to alter some parts of the simulation without having to look at the program code at all. It now also employs the DPME algorithm for full electrostatics, developed by our collaborators at Duke University.

NAMD2 supports a large number of parallel machines, including clusters of workstations, the SGI Origin 200 and Origin 2000, the IBM SP3, the Convex Exemplar, and the Cray T3E. The new structure of the program exhibits improved sequential speed, and better parallel performance [22] on machines with dozens to hundreds of processors. Improved algorithms and parallel efficiency, and the availability of large numbers of processor have resulted in an order of magnitude increase in the speed of simulations.

BTA UNIT: T, D

TITLE: Molecular Visualization: The Program VMD

KEYWORDS: molecular graphics, interactive visualization

Axis I: 9

Axis II: 42

INVEST1: Sergei Izrailev

DEGREE1: M.S.

DEPT1: Department of Physics

NONHOST1:

% BRTP $: 10%

ABSTRACT: VMD is a visualization program developed by the Resource and designed for interactive display and analysis of biomolecular systems [13]. The program is capable of animation, manipulation and analysis of proteins, nucleic acids, lipid membranes and other biological molecules. It supports OpenGL and SGI GL graphics libraries with stereo displays. Moreover, VMD supports output formats for VRML (Virtual Reality Modeling Language) and many popular renderers (RayShade, POV-Ray and Raster3D). VMD can read many different file formats directly and through an interface with the program Babel [58]. The wide variety of methods for rendering and coloring molecules offered by VMD includes VdW, licorice, cartoon and surface models. Animation information can come from a trajectory file or by connecting to a running simulation program, such as NAMD [19, 59]. The VMD scripting language is based on TCL/TK. It may be used to query molecular information, perform analysis and display the results interactively, yielding a powerful base for implementing new methods in structure visualization and analysis. To further method development, the complete C++ source code is freely available to the biomedical community, along with documentation for using and modifying the program. Version 1.2 of VMD runs under most versions of Unix, including IRIX, Linux and Solaris, and will soon be ported to Windows NT. See the VMD home page for more information.*

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

BTA UNIT: T

TITLE: Algorithm Development

KEYWORDS: integration methods, multiple time stepping, mollified pulse method

Axis I: 9

Axis II: 42, 48

INVEST1: Jesus Izaguirre

DEGREE1: M.S.

DEPT1: Department of Computer Science

NONHOST1:

INVEST2: David Hardy

DEGREE2: M.S.

DEPT2: Department of Computer Science

NONHOST2:

% BRTP $: 4%

ABSTRACT: Current emphasis is on integration methods for molecular dynamics that can be incorporated into NAMD. The relatively high cost of fast full electrostatics is reduced in NAMD by a factor of four through the use of Verlet-I/r-RESPA/impulse multiple time stepping, in which the full electrostatics is evaluated only every 4 fs. To further increase the time step for these calculations, the mollified impulse method [60] was devised and implemented for flexible water. The variants of the method tested thus far enable an increase in the longest time step from 4 fs to 6.25 fs without introducing Langevin damping. The cause of the time step barrier at 7 fs is under investigation and possible remedies are being devised. Also begun is work on an optimal choice of the force partitioning for multiple time stepping. Observations suggest that non-linear instabilities limit the time step. A related project is making advances in understanding this phenomenon.

BTA UNIT: T

TITLE: Multi Resolution Description of Biological Systems

KEYWORDS: reduced representation, Kirchhoff equations, DNA loop

Axis I: 2, 9

Axis II: 74g

INVEST1: Alexander Balaeff

DEGREE1: M.S.

DEPT1: Center for Biophysics and Computational Biology

NONHOST1:

% BRTP $: 2%

ABSTRACT: Biological systems often represent macromolecular assemblies that require enormous resources to be simulated by all-atom methods. To simulate such aggregates, one has to use reduced representations of proteins and DNA. One such representation is an elastic rod model of DNA. We applied a classical Kirchhoff system of equations [30] to describe DNA in terms of its center-line, curvatures and twist[*]. We used a continuation method [31] to solve the equations, modifying parameters and boundary conditions from the values for which an exact solution is known to the desired values. A particular challenge was to use the anisotropic model of DNA cross-section, as such representation renders the DNA twist non-uniformly distributed along the center-line. In addition, we modified the equations to include the intrinsic twist and curvatures of DNA. We applied the method to the DNA segment bound by lactose repressor (see the Highlight section of this report). The use of boundary conditions obtained from the crystal structure [25] revealed two possible shapes of the DNA loop. The successful solution of the Kirchhoff system of equations suggests that they may be applied to other biological systems, e.g., DNA wrapped around nucleosomes. Since the bifurcation of the solution to the Kirchhoff equations may pose a problem in future applications, we have modified the equations by extracting the oscillatory component of the solution caused by the intrinsic twist of the DNA.

[*] URL: *http://www.ks.uiuc.edu/Research/pro_DNA/elastic/*

BTA UNIT: T

TITLE: Quantum/Classical Methods

KEYWORDS: hybrid quantum/classical, Pauli repulsion, *ab initio*, "classical" wave functions

Axis I: 2, 9

Axis II: 74c

INVEST1: Michal Ben-Nun

DEGREE1: Ph.D.

DEPT1: The Beckman Institute and Department of Chemistry

NONHOST1:

% BRTP $: 7%

ABSTRACT: We have suggested a procedure for evaluating the Pauli repulsion energy in hybrid quantum/classical (Q/C) treatments that is devoid of any system-specific parameterization and is completely *ab initio* [61]. Previous workers have modeled the purely quantum mechanical effect of Pauli repulsion by augmenting the mixed Q/C Hamiltonian with a van der Waals (vdW) term that prevents the electrostatic collapse of the solute and solvent molecules. The introduction of such a phenomenological term is problematic because "atomic radii" [62, 63] are dependent on both molecular structure and electronic state, implying that the vdW term should be a function of these variables.

We proposed to evaluate the Pauli repulsion energy by associating temporary ("classical") wave functions with the classical region and then exploiting the equivalence of Pauli exclusion and permutational antisymmetry. The computational effort associated with the evaluation of the Pauli repulsion is negligible and therefore the method may readily be extended to large systems. The agreement between the proposed hybrid Q/C method and full quantum mechanical calculations [for the hydrogen-bonded water dimer and for $MgOH^+(H_2O)_n$ (n=1–4) clusters] suggests that the method may be applied to a wide variety of hydrogen-bonded systems.

BTA UNIT: T

TITLE: Evolution of Metabolism

KEYWORDS: evolution, metabolic pathways, sequence-function relationship, phylogenies, graph theory

Axis I: 9

Axis II: 58, 59

INVEST1: Christian Forst

DEGREE1: Ph.D.

DEPT1: The Beckman Institute

NONHOST1:

% BRTP $: 8%

ABSTRACT: The abundance of genomic information by completely sequenced microbial genomes provides a starting point for new insights in the multi-level organization of organisms and their evolution[*]. We take the next step, away from annotating genes by functions of expressed proteins, towards a more comprehensive description of metabolic pathways of proteins acting as enzymes processing substrates [64]. By comparing pathogenic microbes with free living organisms the pathogenicity can be related to functions which are missing in autotrophs. H. influencae and E. coli are a well known example for such relationships. Similar results can be reported for free living B. subtilis and pathogenic Streptococci. This study aids in drug design and disease treatment by interfering with host-interaction factors and pathways of pathogens.

We also pursue the development of methods to construct phylogenies between organisms on the level of metabolic pathways. By a graph-theoretical approach combined with sequence information, pathways of different organisms are related to each other. First results have been obtained by applying this method on pathways related to electron transfer. This suggests the chimeric origin of archaea and thus an early evolution of such pathways [65]. On sequence level and gene cluster organization a closer relationship to bacteria than to eucarya can be reported. These accomplishments open the door for reconstructing the minimal set of genes, regulatory and metabolic pathways of the universal ancestor of all three kingdoms, archaea, bacteria and eucarya.

[*] *URL:http://www.ks.uiuc.edu/Research/METHOD/bioinformatics/*

BTA UNIT: T

TITLE: Computational Facility

KEYWORDS: ATM cluster, parallel computing, visualization, supercomputer, network, graphics

Axis I: 11

Axis II:

INVEST1: Tim Dudek

DEGREE1: B.S.

DEPT1: The Beckman Institute

NONHOST1:

% BRTP $: 15%

ABSTRACT: In the past year the facility* has been upgraded in order to meet our increasing computational and visualization needs. We have expanded our graphics power and capabilities with the addition of a) an HP c200 workstation with fx4 high-performance, stereo-capable 3D graphics and b) an SGI Onyx2 InfiniteReality Rack with eight 195 Mhz R10000 parallel processors sharing one gigabyte of RAM.

The SGI Onyx2 InfiniteReality Rack is our top-end high-performance graphics and computing machine, equipped with eight 195 Mhz R10000 parallel processors sharing one gigabyte of RAM. The Onyx2 drives the 3-D visualization facility and has been integrated into the group's current ATM system and connected to the pre-existing cluster of workstations.

With the acquisition of the Onyx2, which also serves as one of our main computational platforms, our overall computational power has increased substantially. At the same time we also upgraded our four existing HP K9000 four processor machines from 128MB of memory to 256 MB of memory per-processor. A recently ordered SGI Origin200 server with 4 180 MHz processors and 512MB of RAM will be installed by the end of May.

By late summer we are planning to install a Beowulf cluster consisting of eight dual-processor nodes running the Linux operating system and connected via switched 100Mb fast Ethernet. Each node will contain two 400MHz Pentium II processors sharing a 100MHz memory bus to 256MB. Later in the year, the cluster will be upgraded from 8 to 16 nodes. This

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

Beowulf cluster will be a primary target platform for NAMD development as well as for simulation jobs.

This year, as in previous years, the group has been awarded a National Resource Allocations Committee (NRAC) award for computer time at the National Science Foundation funded supercomputer centers. We have been awarded 45,000 service units on NCSA's Origin2000, 100,000 service units on NCSA's Convex Exemplar, and 20,000 Units on PSC's T3E.

BTA UNIT: C

TITLE: Structure and Function of the Bacterial Photosynthetic Unit

KEYWORDS: light harvesting complexes, energy transfer, photosynthesis, purple bacteria, bacteriochlorophyll

Axis I: 7a, 9

Axis II: 74h

INVEST1: Xiche Hu

DEGREE1: Ph.D.

DEPT1: The Beckman Institute

NONHOST1:

INVEST2: Ana Damjanovic

DEGREE2: B.S.

DEPT2: Department of Physics

NONHOST2:

INVEST3: Thorsten Ritz

DEGREE3: B.S.

DEPT3: Department of Physics

NONHOST3:

INVEST4: Michael C. Zerner

DEGREE4: Ph.D.

DEPT4: Quantum Theory Project

NONHOST4: University of Florida

% BRTP $: 5%

ABSTRACT: The photosynthetic unit (PSU) is located in the intracytoplasmic membrane of purple bacteria and consists of two types of pigment-protein complexes:

the photosynthetic reaction center (RC) and light-harvesting complexes (LHs). The LHs capture sunlight and transfer the excitation energy to the RC where it initiates a charge separation process. We have constructed an atomic model of the entire bacterial PSU* consisting of an LH-I–RC complex surrounded by an array of LH-Is through a combination of x-ray crystallography, electron microscopy and molecular modeling [66-70]. This accomplishment opens the door to both spectroscopic and theoretical studies of the pathways of excitation transfer and of the underlying transfer mechanisms in the bacterial photosynthetic membrane.

The excitation transfer pathway can be divided into two steps: intramolecular excitation transfer between pigments within a pigment-protein complex, and intermolecular excitation transfer between different pigment-protein complexes. Within a light-harvesting complex, photons can be absorbed either by carotenoids that instantly transfer their excitation energy to bacteriochlorophylls (BChls), or by BChls themselves. We calculated the couplings between various electronic excitations of carotenoids and BChls through the Pariser-Parr-Pople self-consistent field/CI description of their electronic states, thereby identifying the most probable pathway and dominant mechanism of the excitation transfer between carotenoids and BChls [71].

Excitation transfer between different light-harvesting complexes occurs through the interactions of rings of BChls. The ring-shaped BChl aggregates in LHs were found by quantum chemical and effective Hamiltonian calculations to display coherent excited state properties that are optimal for excitation transfer [70, 72, 73]. On the basis of the effective Hamiltonian description we have determined the excitation transfer rates LH-II $\rightarrow$ LH-I $\rightarrow$ RC for the PSU of Rb. sphaeroides [68, 70, 72], which are in good agreement with spectroscopic measurements. Our quantum calculations have also shed light on the role of the accessory BChls as mediators of excitation transfer from LH-I BChls to the RC special pair.

* *URL:http://www.ks.uiuc.edu/Research/bio_ener/LH_2/*

BTA UNIT: C

TITLE: Structure Refinement and Water Placement in Bacteriorhodopsin

KEYWORDS: bacteriorhodopsin, membrane protein, retinal, photocycle, molecular dynamics, free energy calculations

Axis I: 6, 25g

Axis II: 74h

INVEST1: Jerome Baudry

DEGREE1: Ph.D.

DEPT1: The Beckman Institute

NONHOST1:

INVEST2: Hui Lu

DEGREE2: M.S.

DEPT2: Department of Nuclear Engineering

NONHOST2:

INVEST3: Ferenc Molnar

DEGREE3: Ph.D.

DEPT3: The Beckman Institute

% BRTP $: 2%

ABSTRACT: Bacteriorhodopsin (bR) is a transmembrane protein that functions as a light-driven proton pump in the cell membrane of *Halobacterium salinarium*. The function is achieved through a cyclic process initiated by the absorption of a photon [34]. The pump cycle is characterized by a series of intermediates that differ both spectroscopically and structurally. Water molecules near the chromophore of bR are experimentally known to play an important role in the function of the protein. Recently, a better resolved structure of bR has been reported [47], yet the position of the water molecules is still not well-defined.

Our work* aims at placing the water molecules in the new structure according to thermodynamic criteria [74]. The free energy of solvation is calculated, and the probability of occupation of cavities in the proton channel by one (or

* *URL:http://www.ks.uiuc.edu/Research/bio_ener/bR/*

more) water molecule(s) is calculated. Our simulations indicate that in the new structure, a water molecule located near the Schiff Base, on the extracellular side is very stable, while a water molecule on the cytoplasmic side is less stable. These results differ from the ones obtained using the previous structure [74].

We plan to continue this work and explore other possible hydration sites. The resulting model will be used for quantum mechanical simulations of the primary photo-event.

BTA UNIT: C

TITLE: Oxygen and Proton Pathways in Cytochrome *c* Oxidase

KEYWORDS: proton pumping, water placement, oxygen diffusion

Axis I: 2, 9, 24

Axis II: 30, 46, 74c, 77, 89

INVEST1: Ivo Hofacker

DEGREE1: Ph.D.

DEPT1: The Beckman Institute

NONHOST1:

INVEST2: Hartmut Michel

DEGREE2: Ph.D.

DEPT2: Biochemistry

NONHOST2: Max-Planck-Institute für Biochemie, Frankfurt, Germany

% BRTP $: 2%

ABSTRACT: Cytochrome *c* oxidase is a redox-driven proton pump, which couples the reduction of oxygen to water to the translocation of protons across the membrane. The recently solved x-ray structures of cytochrome *c* oxidase permit molecular dynamics simulations of the underlying transport processes[*]. To eventually establish the proton pump mechanism we investigated the transport of the substrates, oxygen and protons, through the enzyme (see reference [75]).

Molecular dynamics simulations of oxygen diffusion through the protein revealed a pathway to the oxygen binding site starting at a hydrophobic cavity near the membrane exposed surface of sub-unit I, close to the interface to sub-unit III. A large number of water sites was predicted within the protein. We found that the water molecules form two channels along which protons can enter from the cytoplasmic (matrix) side of the protein and reach the binuclear center.

These studies suggest that oxygen is channeled to the catalytic center of the enzyme along a well defined path. Hydrophobic cavities at the start of the

[*] *URL:http://www.ks.uiuc.edu/Research/bio_ener/cco/*

path could serve as reservoirs for oxygen, and water molecules might play an essential role for the transfer of protons in cytochrome c oxidase. A possible pumping mechanism that involves a shuttling motion of a glutamic acid side chain, which could then transfer a proton to a propionate group of heme a3, has been proposed.

BTA UNIT: C

TITLE: Structure Prediction of Apolipoprotein A-I in rHDL Disks

KEYWORDS: HDL, reconstituted discoidal HDL, apolipoprotein A-I, apolipoprotein conformation, POPC, lipid bilayers, protein structure prediction, molecular dynamics simulations

AXIS I: 2, 6, 9

AXIS II: 74f,h; 77

INVEST1: Jim Phillips

DEGREE1: M.S.

DEPT1: Department of Physics

NONHOST1:

INVEST2: Ana Jonas

DEGREE2: Ph.D.

DEPT2: College of Medicine

NONHOST2:

INVEST3: Stephen C. Harvey

DEGREE3: Ph.D.

DEPT3: Department of Biochemistry and Molecular Genetics

NONHOST3: University of Alabama at Birmingham

% BRTP $: 2%

ABSTRACT: High density lipoproteins (HDL) circulate in the blood of vertebrates, transporting cholesterol from various body tissues to the liver for excretion or recycling. HDL particles are protein-lipid complexes of apolipoprotein A-I (apoA-I), several minor proteins, phospolipids, cholesterol, and cholesterol esters. Reconstituted HDL (rHDL), developed in the Jonas lab, have provided the best opportunities to experimentally study the structure-function relationships of apoA-I because of their defined compositions and sizes [76]. Nascent rHDL particles consist of a phospolipid bilayer disk surrounded by two apoA-I molecules. The amphipathic helices of apoA-I shield the hydrophobic lipid tails, solubilizing the rHDL particle in water.

The Harvey group has used NAMD and VMD to carry out and analyze molecular dynamics simulations on a model HDL particle consisting of twenty POPC lipids and twelve synthetic alpha-helical 18-mer peptides with an apolipoprotein-like charge distribution immersed in an appropriate solvent bath [77]. This simulation of 28,552 atoms covered approximately one nanosecond of total time and required several months of CPU time on the Resource computers. Several possible salt bridges between and within helices were studied. Some salt bridges appeared to be stable based on estimated values of ΔG for salt bridge formation.

The structure of rHDL has not been observed experimentally as protein-lipid complexes are extremely difficult to crystallize. Hence, Resource personnel have constructed a model of the lipid-binding domain of apoA-I in rHDL particles[*] based on experimental evidence and sequence analysis [78]. The total system, comprising two apolipoproteins, 160 POPC lipids, and 6,224 water molecules, 46,522 atoms in all, was tested via simulated annealing using NAMD 2 for a total of 250 ps. Future work will focus on improving this current picket-fence model of HDL, as well as incorporating information from a recent lipid-free crystal structure of the apoA-I lipid-binding domain which exhibits in a lipid-free complex of four proteins an alternative belt-like structure [79].

[*] *URL:http://www.ks.uiuc.edu/Research/apoa1/*

BTA UNIT: C

TITLE: Structure Prediction of a Complex Between the Chromosomal Protein HMG-D and DNA

KEYWORDS: molecular dynamics, DNA, protein-DNA interaction, transcription regulation

AXIS I: 9

AXIS II: 74g, 77

INVEST1: Alexander Balaeff

DEGREE1: M.S.

DEPT1: Center for Biophysics and Computational Biology

NONHOST1:

INVEST2: Mair Churchill

DEGREE2: Ph.D.

DEPT2: Department of Cell and Structural Biology

NONHOST2:

% BRTP $: 3%

ABSTRACT: Non-histone chromosomal proteins are an important part of nuclear structure and function due to their ability to interact with DNA, to form and modulate chromatin structure, and to regulate gene expression [80, 81]. However, the understanding of the function of chromosomal proteins at the molecular level has been hampered by the lack of structures of chromosomal protein–DNA complexes. We have carried out a molecular dynamics modeling study* [82] to provide insight into the mode of DNA binding by the chromosomal HMG–domain protein, HMG-D [83, 84]. Three models of a complex of HMG-D bound to DNA were derived through docking the protein to two different DNA fragments of known structure. Molecular dynamics simulations of the complexes provided data indicating the most favorable model. This model was further refined by molecular dynamics simulation and extensively analyzed. The structure of the corresponding HMG-D-DNA complex exhibits many features seen in the NMR structures of the sequence-specific HMG-domain-DNA complexes, lymphoid enhancer factor 1 (LEF-1) [85] and testis determining factor (SRY) [86]. The model reveals differences from these known structures that suggest how chromosomal proteins bind to many different DNA sequences with comparable affinity.

* *URL:http://www.ks.uiuc.edu/Research/pro_DNA/hmgd/*

BTA UNIT: C

TITLE: Probing the Role of Structural Water using DNA with Analogues

KEYWORDS: molecular dynamics simulations, DNA, water, analogues, hydrogen bonding, stacking interactions

AXIS I: 2, 9

AXIS II: 74g,h

INVEST1: Dorina Kosztin

DEGREE1: M.S.

DEPT1: Department of Chemistry

NONHOST1:

INVEST2: Richard Gumport

DEGREE2: Ph.D.

DEPT2: Department of Biochemistry

NONHOST2:

% BRTP $: 2%

ABSTRACT: Crystal structures of DNA and protein–DNA complexes show the existence of "fixed" water molecules in the minor and major groove of DNA and at the protein–DNA interface [87, 88]. We studied the effect of these water molecules on the structure and bending of DNA, as well as on the binding specificity, by using DNA with analogues[*]. It was argued theoretically, and supported experimentally, that a water molecule bridges between the N7 of the purine ring and the exocyclic amino group in adenine bases. The 2'-deoxy-7-hydroxymethyl-7-deazaadenosine analogue (hm^7c^7dA) [89] was suggested to mimic the role of structural water in the major groove of DNA. This analogue replaces the adenine base and the water molecule bound to it.

Four distinct systems, based on the Dickerson dodecamer with d(CGCGAATTCGCG) sequence, were constructed: the dodecamer itself, the dodecamer with both adenine bases at position 5 and 6 mutated, the dodecamer with adenine base at position 5 mutated and the dodecamer with adenine base at position 6 mutated. DNA structure and dynamics are known to be sensitive to hydration, therefore, the DNA was embedded in a

[*] *URL:http://www.ks.uiuc.edu/Research/pro_DNA/ster_horm_rec/*

previously equilibrated cylinder of water molecules. To counterbalance the negative charge on the DNA backbone, 15 sodium ions were added by replacing 15 water molecules with the highest electrostatic energies of the oxygen atom. There are approximately 12,000 atoms in each system. The molecular dynamics program NAMD was used to run the simulations. For each system, 1ns of dynamics was performed: 250 ps of dynamics with soft constraints on the terminal base-pairs of the DNA and 750 ps of free dynamics in order to yield a better hydration of the DNA bases.

The structural deviations of DNA from the initial X-ray crystal structure, evaluated on the basis of root mean square deviations (RMSD) for all four systems, show that the analogue does not affect the overall DNA conformation. Bending points develop in the axis of the DNA at the CG–AA and TT–CG steps in all the simulations. In addition, the analogue does not affect the hydrogen bonding and stacking interactions in either of the simulated structures.

Since the (hm^7c^7dA) analogue does not disrupt the conformation and properties of B-form DNA, the interaction of proteins with DNA containing this analogue will be studied further to better delineate the role of water in protein-DNA interactions. The crystal structure of the trp-repressor bound to DNA [90] will be used as the starting point.

BTA UNIT: C

TITLE: Structure and Dynamics of Calmodulin in Solution

KEYWORDS: regulation, cell motility, muscle contraction, calcium, target peptide

AXIS I: 9, 20

AXIS II: 42, 74c, 77

INVEST1: Willy Wriggers

DEGREE1: M.S.

DEPT1: Department of Physics

NONHOST1:

INVEST2: Harel Weinstein

DEGREE2: Ph.D.

DEPT2: Mount Sinai School of Medicine

NONHOST2: City University of New York

% BRTP $: 2%

ABSTRACT: To characterize the dynamic behavior of calmodulin in solution, we have carried out molecular dynamics (MD) simulations of the Ca^{2+}-loaded structure* (see reference [91]). The crystal structure of calmodulin was placed in a solvent sphere of radius 44Å, and 6 Cl^- and 22 Na^+ ions were included to neutralize the system and to model a 150 mM salt concentration. The total number of atoms was 32,867. During the 3 ns simulation the structure exhibits large conformational changes on the nanosecond time scale. The central alpha-helix, which has been shown to unwind locally upon binding of calmodulin to target proteins, bends and unwinds near residue Arg74. We interpret this result as a preparative step in the more extensive structural transition observed in the "flexible linker" region 74-82 of the central helix upon complex formation. The major structural change is a reorientation of the two Ca^{2+}-binding domains with respect to each other and a rearrangement of alpha-helices in the N-terminus domain which make the hydrophobic target peptide binding site more accessible. This structural rearrangement brings the domains to a more favorable position for target binding, poised to achieve the orientation observed in the complex of calmodulin with myosin-light-chain-kinase. Analysis of solvent structure reveals an inhomogeneity in the mobility

* *URL:http://www.ks.uiuc.edu/Research/cell_motility/calmodulin/*

of water in the vicinity of the protein which is attributable to the hydrophobic effect exerted by calmodulin's binding sites for target peptides.

BTA UNIT: C

TITLE: Modeling of the Structure of an Integral Membrane Protein Aquaporin

KEYWORDS: aquaporin, water channel, protein structure, integral membrane protein, structure prediction

Axis I: 6, 7a

Axis II: 52; 74g,h

INVEST1: Xiche Hu

DEGREE1: Ph.D.

DEPT1: The Beckman Institute

NONHOST1:

INVEST2: Alok K. Mitra

DEGREE2: Ph.D.

DEPT2: Department of Cell Biology

NONHOST2: Scripps Research Institute

% BRTP $: 3%

ABSTRACT: Water is an essential component of all living cells and their extracellular surroundings. Transport of water in and out of cells occurs during a variety of important cellular functions such as regulation of body temperature, elimination of toxins, digestion, respiration, circulation, and neural homeostasis. Aquaporin-1 (AQP1) is an integral membrane protein that functions as a specific and constitutively active water conducting channel [92, 93]. We are attempting to predict the structure of AQP1 from human erythrocyte membranes [94] by means of a hierarchical structure prediction approach. In this approach molecular dynamics simulations and energy minimization are combined with conventional structure prediction methods under experimental constraints derived from biochemical and spectroscopical data.

AQP1 from human erythrocyte is composed of 269 residues [94] that form six transmembrane helices. Hydropathy analysis was performed to identify the putative transmembrane segments, which were then independently verified by multiple sequence alignment propensity analyses and homology modeling. A consensus assignment for secondary structure was derived from combination of all the prediction methods used. Three dimensional structures

for transmembrane helical segments were built by comparative modeling. The resulting tertiary structures were then aggregated into a quaternary structure through molecular dynamics simulations followed by energy minimization under constraints provided by a low resolution three dimensional electron density map measured by electron microscopy [95], site directed mutagenesis and FT Resonance Raman spectra, as well as conservation of residues.

BTA Unit: C

TITLE: Nucleotide-Dependent Movements of the Kinesin Motor Domain Predicted by Simulated Annealing

KEYWORDS: kinesin, ATPase, domain movement, power stroke, back door enzyme

AXIS I: 9, 20

AXIS II: 42, 74c,h; 77

INVEST1: Willy Wriggers

DEGREE1: M.S.

DEPT1: Department of Physics

NONHOST1:

%BRTP $: 2%

ABSTRACT: The structure of an ATP-bound kinesin motor domain has been predicted and conformational differences relative to the known ADP-bound form of the protein were identified,[*] as reported in reference [96]. The differences should be attributed to force-producing ATP hydrolysis. Candidate ATP-kinesin structures were obtained by simulated annealing, by placement of the ATP gamma-phosphate in the crystal structure of ADP-kinesin, and by inter-atomic distance constraints. The choice of such constraints was based on mutagenesis experiments, which identified Gly234 as one of the gamma-phosphate sensing residues, as well as on structural comparison of kinesin with the homologous ncd motor and with G proteins. The prediction of nucleotide-dependent conformational differences reveals an allosteric coupling between the nucleotide pocket and the microtubule binding site of kinesin. Interactions of ATP with Gly234 and Ser202 trigger structural changes in the motor domain, the nucleotide acting as an allosteric modifier of kinesin's microtubule-binding state. We suggest that in the presence of ATP kinesin's putative microtubule binding regions (L8, L12, L11, alpha4, alpha5 and alpha6) form a face complementary in shape to the microtubule surface. In the presence of ADP, the microtubule binding face adopts a more convex shape relative to the ATP-bound form, reducing kinesin's affinity to the microtubule.

[*] *URL:http://www.ks.uiuc.edu/Research/cell_motility/kinesin/*

BTA UNIT: C

TITLE: Force-Induced Unfolding of Titin Immunoglobulin Domains

KEYWORDS: titin, immunoglobulin, muscle protein, elasticity, steered molecular dynamics.

Axis I: 13, 20

Axis II: 74h

INVEST1: Hui Lu

DEGREE1: M.S.

DEPT1: Nuclear Engineering

NONHOST1:

INVEST2: Barry Israelewitz

DEGREE2: M.A.

DEPT2: Center for Biophysics and Computational Biology

NONHOST2:

INVEST3: Andre Krammer

DEGREE3: M.S.

DEPT3: Physics

NONHOST3: University of Washington, Seattle

INVEST4: Viola Vogel

DEGREE4: Ph.D.

DEPT4: Bioengineering

NONHOST4: University of Washington, Seattle

% BRTP $: 3%

ABSTRACT: Titin, a 1μm-long protein (7,800 atoms) found in striated muscle myofibrils, possesses unique elastic and extensibility properties in its I-band region, which is largely composed of a PEVK region and 7-strand β-sandwich

immunoglobulin-like (Ig) domains [50]. The behavior of titin as a multi-stage entropic spring has been shown in atomic force microscopy [54] and optical tweezer experiments to partially depend on the reversible unfolding of individual Ig domains. We performed SMD simulations* to stretch single titin Ig domains in solution with pulling speeds of 0.5 and 1.0Å/ps [7]. The resulting force-extension profiles exhibit a single dominant peak for each Ig domain unfolding, consistent with the experimentally observed sequential, as opposed to concerted, unfolding of Ig domains under external stretching forces. This force peak can be attributed to an initial burst of backbone hydrogen bonds, which takes place between anti-parallel β-strands A and B and between parallel β-strands A' and G. Additional features of the simulations, including the position of the force peak and relative unfolding resistance of different Ig domains, can be related to experimental observations.

Similar elastic behavior is also found in other protein domains, such as tenascin fibronectin-III-like domains. Simulations of fibronectin-III domain unfolding, and of unfolding of two connected Ig domains, are currently ongoing.

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

BTA UNIT: C

TITLE: Investigation of the Conformational Changes Involved in the Electron Transfer in Cytochrome bc_1 Complexes

KEYWORDS: bioenergetics, electron transfer, steered molecular dynamics

Axis I: 2, 9

Axis II: 74h

INVEST1: Sergei Izrailev

DEGREE1: M.S.

DEPT1: Department of Physics

NONHOST1:

INVEST2: Anthony R. Crofts

DEGREE2: Ph.D.

DEPT2: Center for Biophysics and Computational Biology

NONHOST2:

INVEST3: E. A. Berry

DEGREE3: Ph.D.

DEPT3:

NONHOST3: Lawrence Berkeley National Laboratory

% BRTP $: 2%

ABSTRACT: The ubiquinol cytochrome *c* oxidoreductase (cytochrome bc_1 complex) plays a central role in electron transport chains of bacteria, mitochondria and chloroplasts, converting redox free energy into a proton gradient used to drive the cell's metabolism through ATP synthesis. This complex catalyzes the oxidation of ubiquinol in the membrane, the reduction of cytochrome *c* and the translocation of protons across the membrane [97]. All bc_1 complexes contain three essential sub-units to which the prosthetic groups are bound: a cytochrome (cyt) *b* with high- and low-potential hemes b_H and b_L, an iron sulfur protein (ISP) containing a 2Fe2S center, and a cytochrome c_1 with another heme group. The catalytic mechanism involves two catalytic sites for oxidation (O_o site) or reduction (O_i site) of the quinones.

The crystal structures of several mitochondrial bc_1 complexes with and without an inhibitor (stigmatellin) bound at the O_o site became available during the past year [98, 99]. In the structure with stigmatellin bound, part of the ISP domain is turned with respect to its position in the structure without the inhibitor [99]. This suggests that the electron transfer path from the O_o site to cyt c_1 involves a substantial movement of the ISP. Our collaborator, A. R. Crofts, provided us with crystal structures of chicken heart mitochondria bc_1 complexes, with and without the inhibitor bound at the O_o site [99]. Comparison of these two structures revealed the axis of rotation of the iron sulfur protein (ISP) mobile head and the angle of rotation. We have prepared two systems consisting of the cytochrome *b*, cytochrome c_1 and ISP domains of the two structures for equilibration.

We investigate the mechanism governing the rotation of the ISP head by means of Steered Molecular Dynamic (SMD) simulations [3-8, 100]. In the simulations, external forces have to be applied to the ISP to provide an appropriate torque inducing the rotation. We are mainly interested in revealing the geometrical constraints imposed on the movement of the ISP head by the other sub-units of the bc_1 complex. We will simulate the rotation of the ISP head in the presence of cyt *b* and cyt c_1 sub-units by using SMD to induce the rotation. This simulation will provide the information on whether the motion of the ISP head is unconstrained or it involves molecular interactions that may induce or prevent the rotation. The latter case may indicate mutations that alter the rate of the catalytic reaction.

BTA UNIT: C

TITLE: Extraction of Lipids from Membranes

KEYWORDS: phospholipase A2, steered molecular dynamics

AXIS I: 2, 6

AXIS II: 74f

INVEST1: Sergei Izrailev

DEGREE1: M.S.

DEPT1: Department of Physics

NONHOST1:

INVEST2: Sergey Stepaniants

DEGREE2: Ph.D.

DEPT2: The Beckman Institute

NONHOST2:

% BRTP $: 2%

ABSTRACT: Phospholipase A2 (PLA2) is a protein (16,000 atoms) which complexes with membrane surfaces, destabilizes a phospholipid, extracts it from the membrane, and catalyzes the hydrolysis reaction of the *sn*-2-acyl chain of the lipid [14-16]. One of the reaction products, arachidonic acid, is an important metabolic intermediate producing eicosanoids, which are regulatory factors implicated in a wide range of physiological and pathological states [101]. The interfacial catalysis of PLA2 involves four reaction steps: complex formation, scooting on the surface, lipid extraction from the membrane, and the hydrolysis reaction. We had previously modeled the formation of the complex of human synovial phospholipase A2 with a membrane [102]. Steered molecular dynamics simulations [3, 4, 6, 8, 100] were employed to investigate the lipid extraction step by pulling a lipid molecule from a monolayer of dilauroyl-phosphatidyl-ethanolamin (DLPE) lipids into the active site of PLA2 and into the aqueous phase[*] [5]. External forces were applied to the head group of the lipid, pulling it out from the membrane.

The forces required to displace the lipid from the membrane into the binding pocket of PLA2 were larger than those required to displace the lipid from the membrane into the aqueous phase. The simulations showed that in the

[*] *URL:http://www.ks.uiuc.edu/Research/METHOD/force_pull/*

presence of PLA2 the hydrogen bonds are formed between the phosphate and amino groups of the extracted lipid and the corresponding groups of the neighboring lipids. These bonds had to be broken in order to extract the lipid from the monolayer. In the absence of PLA2, however, the lipid head groups were well solvated and did not form hydrogen bonds with each other. These results do not agree with the hypothesis of destabilization of the lipids by PLA2, facilitating lipid extraction by the enzyme. The disagreement may have resulted from the steric effects mentioned above, an imperfect choice of the pulling direction for the lipid extraction into the enzyme, or insufficient sampling due to the short (500 ps) simulation time.

BTA UNIT: C

TITLE: Binding Pathway of Arachidonic Acid in Prostaglandin H_2 synthase-1

KEYWORDS: ligand binding, arachidonic acid, prostaglandin H_2 synthase-1, cyclooxygenase-1

Axis I: 2

Axis II: 74f

INVEST1: Ferenc Molnar

DEGREE1: Ph.D.

DEPT1: The Beckman Institute

NONHOST1:

INVEST2: Lawrence S. Norris

DEGREE2: M.S.

DEPT2: Departments of Biomedical Engineering and Chemistry

NONHOST2: Northwestern University

% BRTP $: 2%

ABSTRACT: The enzyme prostaglandin H_2 synthase-1 (PGHS-1) catalyzes the transformation of the essential fatty acid, arachidonic acid (AA), to prostaglandin H_2 [17]. Aspirin, flurbiprofen, and other non-steroidal anti-inflammatory drugs directly target PGHS-1 and inhibit the first step of its transformation by preventing access of AA to the cyclooxygenase active site. Based on the crystal structure of PGHS-1, with flurbiprofen bound at the active site, a model for AA embedded in the enzyme has been suggested, in which AA replaces the inhibitor [18]. The aim of the investigation is to elucidate the folding of AA into the narrow hydrophobic binding channel of the cyclooxygenase site, and to identify key residues guiding AA binding.

Steered Molecular Dynamics calculations (SMD) [3-8, 103, 104] of enforced unbinding were carried out on one monomer (9,000 atoms) of the PGHS-1 homo-dimer with AA bound in its putative cyclooxygenation site, leading to the exit of the ligand from its narrow hydrophobic binding channel[*]. AA contains four rigid *cis* double bonds connected to each other by a pair of conformationally flexible single bonds. The unbinding mechanism can be described as a series of rotations around these single bonds that leave the

[*] *URL:http://www.ks.uiuc.edu/Research/pghs/*

"rigid backbone" of the fatty acid formed by the conformationally inflexible *cis* double bonds relatively unaffected. Our hypothesis is that this type of concerted motion is specific for the chemical structure of AA and is important for the binding and recognition mechanism.

Another set of simulations was carried out with the Targeted Molecular Dynamics (TMD) method [105]. A comparison of the SMD and TMD simulations revealed that the pathways generated by both methods show very similar modes of concerted rotations around single bonds during the unbinding of AA.

BTA UNIT: C

TITLE: Modeling Ligand Binding to Nuclear Hormone Receptors

KEYWORDS: retinoic acid, steered molecular dynamics, hormone binding, unbinding pathways, force

Axis I: 2, 9

Axis II: 74e,h

INVEST1: Dorina Kosztin

DEGREE1: M.S.

DEPT1: Department of Chemistry

NONHOST1:

INVEST2: John Katzenellenbogen

DEGREE2: Ph.D.

DEPT2: Department of Chemistry

NONHOST2:

% BRTP $: 2%

ABSTRACT: Retinoic acid (t-RA) is an important regulator of cell growth and differentiation in both the adult and developing embryo. The effects of t-RA are mediated through the retinoic acid receptor (RAR) that binds all-*trans*-RA (t-RA) but the underlying mechanism is still not known [106]. Using Steered Molecular Dynamics (SMD) [100] we studied the transition between the bound and unbound form of the retinoic acid receptor, known from experiment to be accompanied by a conformational change that enables the hormone–receptor complex to bind to specific sequences of DNA and other transcriptional coactivators or repressors[*]. The crystal structure of the ligand binding domain (the receptor domain responsible for recognizing and binding the hormone) of the human retinoic acid receptor hRAR-γ bound to all-*trans* retinoic acid [107] was used for simulating different unbinding pathways. Examination of the crystal structure of the hRAR-γ bound to t-RA suggests three entry/exit points for the hormone that were explored using SMD. In all simulations, the protein–ligand system was surrounded by a water bath, the total number of atoms being ≈15,000. One atom of the hormone was harmonically restrained (K=10 kcal $mol^{-1}/Å^2$) to a point

[*] *URL:http://www.ks.uiuc.edu/Research/pro_DNA/ster_horm_rec/*

moving with a constant velocity v=0.032 Å/ps in a chosen direction. The molecular dynamics program NAMD [19], was used to compute three different trajectories of 750 ps each. The results of our simulations show that, if strong enough forces are applied, it is possible to extract the hormone out of the binding pocket, with little or almost no effect on the protein structure. Along one of the pathways the hormone has to overcome the strong electrostatic forces between its carboxylate group and the charged Lys and Arg residues lining the opening. In the other two cases, before the hormone is completely out of the protein, the carboxylate group of the hormone interacts strongly with some of the neighboring residues. It may indicate that those residues are the ones to attract and guide the hormone toward the binding pocket. Further studies of the unbinding mechanism will be conducted using the Targeted Molecular Dynamics (TMD) method [105]. TMD imposes time-dependent holonomic constraints that drive the system from the bound to the unbound state. The resulting pathways may be used for choosing the direction of the applied force in SMD simulations.

	TECH RES & DEVEL (T)	COLLAB RES & SERVICE (C)	DISSEM & TRAINING (D)	TOTALS
NUMBER OF PUBLICATIONS	25	28	1	54
NUMBER OF SUBPROJECTS	7	14	2	23*
NUMBER OF INVESTIGATORS	11	28	5	44*
PERCENT OF BRTP FUNDS ALLOCATED	56%	34%	10%	100%
SERVICE FEES COLLECTED	0	0	0	0
OTHER FUNDS ($)	640,000	10,000 133,000	—	783,000

* Investigators and subprojects classified to more than one BRTP unit are counted twice.

State or Country	Number of Investigators
IL	28
NY	1
WA	2
CA	2
AL	1
Germany	1

BRTP Unit T

Investigator	Non-Host Institution (Principle Investigator)	Sources of Support	
		TYPE	AGENCY
Balaeff, Alexander	University of Illinois (Schulten, Klaus)	OTH	
Ben-Nun, Michal	University of Illinois (Martinez, Todd)	FED	NIH
Bhandarkar, Milind	University of Illinois (Kale, Laximkant)	FED	NSF
Brunner, Robert	University of Illinois (Kale, Laximkant)	FED	NIH
Dudek, Tim	University of Illinois (Schulten, Klaus)	FED	NIH
Forst, Christian	University of Illinois (Schulten, Klaus)	FED	NIH
Hardy, David	University of Illinois (Skeel, Robert)	FED	NIH
Izrailev, Sergei	University of Illinois (Schulten, Klaus)	OTH	
Izaguirre, Jesus	University of Illinois (Skeel, Robert)	FED	NSF
Phillips, Jim	University of Illinois (Schulten, Klaus)	FED	DOE
Varadarajan, Krishnan	University of Illinois (Kale, Laximkant)	FED	NIH

BRTP Unit C

Investigator	Non-Host Institution (Principle Investigator)	Sources of Support	
		TYPE	AGENCY
Balaeff, Alexander	University of Illinois (Schulten, Klaus)	OTH	
Baudry, Jerome	University of Illinois (Schulten, Klaus)	FED	NIH
Berry, E. A.	Lawrence Berkeley National Laboratory (Berry, E. A.)	FED	DOE
Churchill, Mair	University of Illinois (Churchill, Mair)	OTH	
Crofts, Anthony	University of Illinois (Crofts, Anthony)	FED	NIH
Damjanovic, Ana	University of Illinois (Schulten, Klaus)	OTH	
Gumport, Richard	University of Illinois (Gumport, Richard)	FED	NIH
Harvey, Stephen	University of Alabama at Birmingham (Harvey, Stephen)	FED	NIH
Hofacker, Ivo	University of Illinois (Schulten, Klaus)	FED	NSF
Hu, Xiche	University of Illinois (Schulten, Klaus)	OTH	
Isralewitz, Barry	University of Illinois (Schulten, Klaus)	OTH	
Izrailev, Sergei	University of Illinois (Schulten, Klaus)	OTH	
Jonas, Ana	University of Illinois (Jonas, Ana)	FED	NIH
Katzenellenbogen, John	University of Illinois (Katzenellenbogen, John)	FED	NIH
Kosztin, Dorina	University of Illinois (Schulten, Klaus)	OTH	
Krammer, Andre	University of Washington, Seattle (Vogel, Viola)	FED	NIH
Lu, Hui	University of Illinois (Schulten, Klaus)	FED	NSF

Michel, Hartmut	Max-Planck-Institute für Biochemie, Germany (Michel, Hartmut)	FED	NIH
Mitra, Alok	Scripps Research Institute (Mitra, Alok)	FED	NIH
Molnar, Ferenc	University of Illinois (Schulten, Klaus)	FED	NSF
Norris, Lawrence	Northwestern University (Ratner, Mark)	FED	NIH/NSF
Phillips, Jim	University of Illinois (Schulten, Klaus)	FED	DOE
Ritz, Thorsten	University of Illinois (Schulten, Klaus)	FED	NIH
Vogel, Viola	University of Washington, Seattle (Vogel, Viola)	FED	NIH
Weinstein, Harel	Mount Sinai School of Medicine, CUNY (Weinstein, Harel)	FED	NIH
Wriggers, Willy	University of Illinois (Schulten, Klaus)	FED	NIH
Stepaniants, Sergey	University of Illinois (Schulten, Klaus)	OTH	
Zerner, Michael	University of Florida (Zerner, Michel)	FED	NSF

BRTP Unit D

Investigator	Non-Host Institution (Principle Investigator)	Sources of Support	
		TYPE	AGENCY
Bhandarkar, Milind	University of Illinois (Kale, Laximkant)	FED	NSF
Brunner, Robert	University of Illinois (Kale, Laximkant)	FED	NIH
Phillips, Jim	University of Illinois (Schulten, Klaus)	FED	DOE
Varadarajan, Krishnan	University of Illinois (Kale, Laximkant)	FED	NIH
Izrailev, Sergei	University of Illinois (Schulten, Klaus)	OTH	

BTA unit: (T)

NUMBER PUBLISHED –
Books: 0 Papers: 14 Abstracts: 0

NUMBER IN PRESS OR SUBMITTED –
Books: 0 Papers: 11 Abstracts: 0

Books
PUBLISHED:
None

IN PRESS OR SUBMITTED:
None

Papers
PUBLISHED:

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Abstracts

PUBLISHED:
None

IN PRESS OR SUBMITTED:
None

BTA unit: (C)

NUMBER PUBLISHED –
Books: 0 Papers: 13 Abstracts: 7

NUMBER IN PRESS OR SUBMITTED –
Books: 0 Papers: 8 Abstracts: 0

Books
PUBLISHED:
None

IN PRESS OR SUBMITTED:
None

Papers
PUBLISHED:

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A. Damjanovic, T. Ritz, K. Schulten, "Light-harvesting and photoprotection by carotenoids in photosynthesis," *Biophys. J.* **74**, A76 (1998).

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H. Lu, B. Isralewitz, A. Krammer, V. Vogel, and K. Schulten, "Unfolding of titin immunoglobulin domains by steered molecular dynamics simulation," *Biophys. J.* **74**, A275 (1998).

J.C. Phillips, W. Riggers, Z. Li, A. Jonas, K. Schulten, "Predicting the structure of apolipoprotein A-I in complex with lipids (rHDL disk)," *Biophysical Journal* **74**, A305 (1998).

S. Stepaniants, and K. Schulten, "Applications of steered molecular dynamics to protein-ligand/membrane binding," *Biophys. J.* **74**, A177 (1988).

W. Wriggers and K. Schulten, "Nucleotide-dependent movements of the kinesin motor domain predicted by simulated annealing," *Biophys. J.* **74**, A244 (1998).

IN PRESS OR SUBMITTED:
None

BTA unit: (D)

NUMBER PUBLISHED –
Books: 0 Papers: 0 Abstracts: 0

NUMBER IN PRESS OR SUBMITTED –
Books: 0 Papers: 1 Abstracts: 0

Books
PUBLISHED:
None

IN PRESS OR SUBMITTED:
None

Papers
PUBLISHED:
None

IN PRESS OR SUBMITTED:

M. Bailey, K. Schulten, & J. E. Johnson, "The Use of Solid Physical Models for the Study of Macromolecular Assembly," *Current Opinion in Structural Biology*, in press.

Abstracts
PUBLISHED:
None

IN PRESS OR SUBMITTED:
None

Advisory Committee

As part of the rebuilding efforts we have embarked on during the past year we have also sought to reach a closer fit between the shifting focus and direction of the Resource research and development activities and the areas represented by the board members. Thus, in recent months several of the previous members retired and two new members agreed to join.

Our present six-member advisory board includes esteemed scientists from a multitude of disciplines:

- Theoretical Chemistry – Attila Szabo, NIH, Laboratory of Chemical Physics
- Biophysics – Colin Wraight, School of Life Sciences, UIUC
- Computational Physics – Bernie Alder, Lawrence Livermore Lab, Division of Computational Physics
- Computer Science – William Gear, President, NEC Research Inst.
- Structural Biology – Joel Berendzen, Los Alamos National Laboratory, Physics Division
- Mathematics and Scientific Administration – Peter Arzberger, Associate Director, Office of Advanced Scientific Computing

We intend to convene the board at C-U in early September 1998 and are waiting to hear from the members before finalizing the date.

Dissemination

The Resource continues to fully benefit from the wide array of communication and dissemination tools available today. All software manuals and documentation are posted on our web site, as well as images and results of recent work (*http://www.ks.uiuc.edu/*); research and development accomplishments are published in professional journals and are posted on the web; lectures and talks describing the Resource activities are given all over the world; various documents such as reports and brochures, are periodically mailed to colleagues, prospective members, and federal offices, and are posted on the web (*http://www.ks.uiuc.edu/Publications/*). Videotapes, slides and CDs are made in response to requests from funding agencies, collaborative groups, local administrators and users. The staff continuously reports key findings and systematically disseminates new knowledge produced by the Resource.

The Resource's web site (*http://www.ks.uiuc.edu/*) presents the group's scientific efforts to the outside world. The external web site is accessible to all Internet users. The site includes both scientific and administrative information such as software and hardware available, current research projects, main research accomplishments, image gallery, movie gallery, publication list with abstracts, the people in the group, as well as our seminar series, special events organized by the Resource, job announcements, training and learning opportunities, and more. A search of the web indicates that there are over 500 links to our web pages and it is highly visited. Over the past year our web pages had been visited, on the average, 5,000 times per month.

The principal instrument for the dissemination of software tools and information on prototype modeling projects and related activities is the Resource's web site (*http://www.ks.uiuc.edu/*). The components of MDScope, NAMD and VMD, are freely available in source form, on the Resource's anonymous ftp site at *ftp.ks.uiuc.edu*. VMD and NAMD are accompanied by a User's Guide for general users, and a Programmer's Guide for those who want to modify the programs. Additional information is available on the MDScope web pages, at *http://www.ks.uiuc.edu/Research/mdscope/*. To date, there have been over 4,300 downloads of VMD and over 1,400 of NAMD. We provide user support through email. Over the last 12 months there have been 300 queries from 200 different users. The Resource is dedicated to the development of software that can be used and modified by other researchers. By releasing readily extensible software for general use, others can concentrate on adding the specific features needed on top of a well-developed base, instead of having to re-implement the same features. In this way, third-party users can make their own modifications as appropriate and contribute their own results back to the MDScope effort.

Online newsgroups have been a major channel for the dissemination of MDScope. Newsgroups used for dissemination include:

- bionet.molbio.proteins
- bionet.molec-model
- bionet.biology.computational
- comp.sys.sgi.announce (VMD only)
- bionet.announce

- bionet.software
- comp.lang.tcl.announce (VMD only)

The images in the Resource web and the movie galleries reflect the main areas of the Resource activities (*http://www.ks.uiuc.edu/Overview/gallery/* and *http://www.ks.uiuc.edu/Overview/movie/gallery/*). The "collections" are continuously updated.

During the past year the Resource has published and/or submitted 54 scientific papers (see Books/Papers/Abstracts section of this report). The Resource also makes its publications available as preprints and reprints in the form of Technical Reports. The manuscripts are maintained in a data base accessible to Resource members and are made available upon request (*http://www.ks.uiuc.edu/Publications/Papers/*).

The Resource maintains a slide library containing images representative of the group research efforts. The slides are used for presentations by Resource staff and by university and federal administrators. The slides also serve as a source of visual information in discussions with collaborators and other scientists.

The PI has presented the following lectures during the past year:

- June 18, 1997, Department of Physics, University of Illinois; REU Lecture: *How Nature Harvests Sunlight*
- July 14-16, 1997, 11th International Conference on Application-specific Systems Architectures and Processors, Federal Institute of Technology, Zurich, Switzerland; Lecture: *A Visual Computing Environment for Very Large Scale Biomolecular Modelling*
- July 16, 1997, University of Basel, Basel, Switzerland; Lecture: *Investigations of the Mechanism of Bacteriorhodopsin by Molecular Dynamics and Quantum Chemistry*
- July 18-28, 1997, 11th International Conference on Dynamical Processes in Excited States of Solids Mittelberg, Kleinwalsertal; Lecture: *Excitation Transfer Pathways in the Chlorophyll-Carotenoid–Aggregates of the Photosynthetic Unit of Purple Bacteria*
- September 7-11, 1997, ACS meeting, Las Vegas, NV; Lecture: *Investigations of the Mechanism of Bacteriorhodopsin by Molecular Dynamics and Quantum Chemistry*
- September 11-14, 1997, Colloquium on Computational Biomolecular Science, National Academy of Sciences, Irvine, CA; Lecture: *The Evolution of Efficient Light Harvesting in Photosynthesis – One Goal, Many Solutions*
- October 3-11, 1997, Third Australian Molecular Modelling Workshop, Melbourne, Australia; Lecture: *Chromophore Organization and Transfer of Electronic Excitation in the Photosynthetic Unit of Purple Bacteria* and Lecture: *Investigations of the Mechanism of Bacteriorhodopsin by Molecular Dynamics and Quantum Chemistry* and Tutorial: *VMD Demonstration*

- November 24, 1997, University of Alabama at Birmingham; Lecture: *Structures and Mechanisms of the Membrane-Bound Light Harvesting Proteins of Photosynthetic Purple Bacteria*
- January 14, 1998, University of Munich, Munich, Germany; Lecture: *Exploring Biomolecules Through Steered Molecular Dynamics/From Newton to Langevin/From Enzyme to Muscle*
- January 18, 1998, 33rd Winter Seminar, Klosters, Switzerland; Lecture: *Exploring Biopolymers Through Steered Molecular Dynamics/From Newton to Langevin/From Reactant to Product/From Enzyme to Muscle/From Theory to Experiment*
- February 26, 1998 NIH Bioengineering Workshop; Poster: *Macromolecular Modeling and Bioinformatics: Computers meet Bioengineering Challenges*
- March 18, 1998, American Physical Society, Los Angeles, CA; Lecture: *Structure and Excitation Transfer Pathways in the Chlorophyll-Carotenoid Aggregate of the Photosynthetic Unit of Purple Bacteria*
- March 24, 1998, Workshop on the Structure of Biological Macromolecules, Trieste, Italy; Lecture: *Structure and Function of a Protein Aggregate – the Light Harvesting Complexes of Purple Bacteria in their Organization in the Photosynthetic Apparatus*
- April 20, 1998,International Colloquium on Computational Chemistry and the Living World, Chambery, France; Lecture: *Evolution of Efficient Light Harvesting in Photosynthesis - One Goal, Many Solutions*
- May 17, 1998, 83rd Dahlem Workshop on Simplicity and Complexity in Proteins and Nucleic Acids, Berlin, Germany; Lecture: *From Complexity to Simplicity: How Nature Organizes Light Harvesting in Photosynthesis*

During the past year the PI served on the following committees:

- Appointments and Promotions Committee, Physics Department, UIUC
- Biotechnology Center Advisory Committee Member, UIUC
- Department of Physics Qualifying Examination Committee, UIUC
- Research Resource Committee, UNC
- Beckman Institute External Advisory Committee
- Biomaterials Ad Hoc Steering Committee
- Beckman Foundation Research Technologies Initiative panelist
- Reviewer for Journal of Physical Chemistry, Biophysical Journal, Nucleic Acids Research Journal, Journal of Chemical Physics, National Institutes of Health, National Science Foundation, International Journal of Quantum Chemistry, Biochimica et Biophysica Acta, IEEE Transactions on Neural Networks, Science, American Chemical Society, Protein Engineering, Folding & Design, Neural Networks.

During the past year Resource members participated and/or presented contributions at the following meetings and institutions:

- Second International Symposium Algorithms for Macromolecular Modelling, Berlin, Germany (R. Skeel, J. Phillips)
- Midwestern Theoretical Computational Chemistry Conference, Beckman Institute, Urbana, Illinois (D. Kosztin, A. Damjanovic, T. Ritz, X. Hu)
- Bioinformatics, Structure, Function (Pfizer Symposium), Beckman Institute, Urbana, Illinois (J. Phillips, S. Izrailev, B. Isralewitz, D. Kosztin)
- NSF-CBMS Conference NA of Hamiltonian Dif. Eqs, Colorado School of Mines, Golden, Colorado (R. Skeel)
- International Conference on Parallel and Distributed Processing Techniques and Applications, Las Vegas, Nevada (L. Kale)
- BMW Research, Munich/Daimler-Benz Systems Technology, Berlin/University of Frankfurt (M. Zeller)
- Summer School on Complex Systems, The Santa Fe Institute, Santa Fe, NM (I. Logunov)
- Computational Science Graduate Fellowship Fellows Conference, Washington, DC (J. Phillips)
- 1997 IEEE International Symposium on Computational Intelligence in Robotics and Automation, Monterey, CA (M. Zeller)
- 10th Intl. Workshop on Languages and Compilers for Parallel Computing, Minneapolis, Minnesota (L. Kale, R. Brunner)
- Scientific Computing and Differential Equations conference, University of Trieste and visit to Janezic's lab in Llubjana (R. Skeel)
- Colloquium on Computational Biomolecular Science, National Academy of Sciences, Irvine, California (W. Wriggers)
- 10th Annual Molecular Biophysics Research Symposium on September 27, 1997, Urbana, Illinois (B. Isralewitz)
- 23rd Midwestern Photosynthesis Conference, Turkey Run, Indiana (T. Ritz, A. Damjanovic)
- Institute of Biophysics, University of Ulm, Germany (T. Ritz)
- 7th Western Photosynthesis Conference, Monterey, CA (A. Damjanovic)
- America Biophysical Society meeting, Kansas City, MO (A. Balaeff, A. Damjanovic, B. Isralewitz, S. Izrailev, D. Kosztin, H. Lu, J. Phillips, T. Ritz, Z. Sun)
- IEEE Computer Society, International Parallel Processing Symposium, Orlando, FL (L. Kale, Milind A. Bhandarkar, R. Brunner)
- Okazaki COE Conference on Molecular Science of Excited States and Nonadiabatic Transitions, Okazaki, Japan (T. J. Martinez)

- American Physical Society meeting, Los Angeles, CA (Xiche Hu)

Service

The services we offer may be classified into two broad categories: technological services, designed to provide the scientific community with easy access to the Resource's software and hardware technology; general services which focus on creating new collaborations, sharing the knowledge and expertise produced by existing collaborations, and ongoing application projects with other biomedical scientists.

Technological Service

A new beta version of VMD1.2 was released on May 12 1998, and a release of the full production version is scheduled for early summer 1998. The new version will offer new features, among them:

- A new platform-Solaris 2
- Upgrade to HP-UX 10
- Upgrade to RedHat Linux 5.0, kernel version 2.0.32
- Upgrade to Tcl/Tk 8.0
- Upgrade to babel 1.6
- Support for MSMS, a program for calculating molecular surfaces
- Support for Grasp file format
- More help accessible from within the program

In the past year VMD was announced and presented in several meetings, key academic, federal and industry websites, and publications, among them in Nature ('New on the Market', October 9, 1997), NIH, SGI. In recent months we started discussions with the leading Cambridge Crystallographic Data Centre (*www.ccdc.cam.ac.uk*) to explore a possible collaboration. The discussions were initiated by CCDC's Executive Director who stated that they "*are extremely impressed with VMD from a user's point of view, and with the quality of the code and documentation. The graphics, functionality and customizability are all superb, and we congratulate you and your colleagues on a very impressive package*" (see Appendix 1). The CCDC is interested in extending VMD to the visualization of small-molecules, particularly their packing motifs, and in bringing VMD capabilities to the attention of small-molecule specialists worldwide. We estimate that the number of VMD active users in the past year exceeded 1,000.

A beta version of NAMD2, the new generation of our MD software, was released in February 1998. New features include:

- Faster sequential performance
- Better parallel speedup

- More machines (HP, Linux, Origin2000, IBM SP3, Sun/Solaris, Cray T3E, Convex Exemplar)
- Periodic boundary conditions
- Triple-time-stepping
- Steered MD
- Constant pressure simulation
- Particle-mesh Ewald electrostatics
- Tcl-based scripting for forces and analysis

We estimate that the number of NAMD active users is over 50. Both VMD and NAMD2 will be licensed by the end of summer 1998 to allow a more systematic monitoring of the pattern of use and a closer tracking of our users' needs, as well as to facilitate clarification and protection of intellectual rights. The programs (binaries and source code) will continue to be freely distributed.

A new VMD CD has been produced and will be distributed to interested users for a fee to recover the costs. A copy of the CD is enclosed with this report

In the past year there have been over 1,700 downloads of VMD and over 840 of NAMD. Since the recent release of VMD1.2 the program has been downloaded over 100 times.

The searchable VMD and NAMD manuals are regularly maintained, and are available on our web site. In the past year the VMD and other Resource web pages have been accessed, on the average, 5,000 hits/month. The MDSCOPE web page is located at *http://www.ks.uiuc.edu/Research/mdscope*.

The MDScope "helpline" is extensively used and over 300 queries from active users were answered in the past year. Messages sent to *namd@ks.uiuc.edu*, *vmd@ks.uiuc.ed*u, or *mdscope@ks.uiuc.edu.* are answered within a business day.

VMD demonstrations and presentations have been offered this year mostly on-campus, including at the NCSA Alliance 98 meeting (April 1998). A VMD tutorial was offered at the Third Australian Molecular Modeling Workshop, Melbourne, Australia, October 1997 and was a great success. More tutorials, traditional and online, are planned for the coming year.

The Resource's workstation clusters are presently used by over 50 external users from both on-campus groups and outside users. Regular external use consumes, on average, 20% of the Resource total disk space.

The Resource has hosted visitors from collaborative groups and others in the past funding period. Recent visitors include:

– **Andre Krammer**, University of Seattle (Summer 97)

– **David Hurwitz**, Department of Chemistry, University of North Carolina (Spring 98)

– **Andre Krammer**, University of Seattle (Spring 98)

– **Zhirong Sun**, Qing Hua University, Beijing, China (Spring 98)

Papers and manuscripts citing work performed with VMD and NAMD in the past year include the following:

VMD CITATIONS

Balaeff A., Churchill M.E.A., Schulten K., "Structure prediction of a complex between the chromosomal protein HMG-D and DNA" *Proteins* **30**, 113-135 (1998).

Bishop T.C., Kosztin D., and Schulten K., "How Hormone Receptor–DNA Binding Affects Nucleosomal DNA: The Role of Symmetry" *Biophys. J.* **72**, 2056-2067 (1997).

Branchini B.R., Nemser A.R., Zimmer M., "A computational analysis of the unique protein-induced tight turn that results in post-translational chromophore formation in green fluorescent protein" *J. Amer. Chem. Soc.* **120**, 1-6 (1988).

Debnath, A.K., "A 'Fragment Fitting Approach' to model disulfide loops by utilizing homologous peptide fragments from unrelated proteins of known structures: Application to the V3 loop of the HIV-1 envelope glycoprotein gp120" *J. Mol. Model.* **3**, 31-47 (1997).

Flower, D.R., "ALTER: Eclectic management of molecular structure data" *J. Mol. Graph. Model.* **15**, 161 (1997).

Gajhede M., Schuller D.J., Henriksen A., et al., "Crystal structure of horseradish peroxidase *c* at 2.15 angstrom resolution" *Nat. Struct. Biol*. **4**, 1032-1038, (1997).

Haney P., Konisky J., Koretke K.K., et al., "Structural basis for thermostability and identification of potential active site residues for adenylate kinases from the archaeal genus *Methanococcus*" *Proteins* **28**, 117-130, (1997).

Hofacker I., Schulten K., "Oxygen and proton pathways in cytochrome c oxidase" *Proteins* **30**, 100-107, (1998).

Hu X.C., Ritz T., Damjanovic A., and Schulten K., "Pigment organization and transfer of electronic excitation in the photosynthetic unit of purple bacteria" *J. Phys. Chem.* **101B,** 3854-3871, (1997).

Ihlenfeldt W.D., "Virtual reality in chemistry" *J. Mol. Model.* **3**, 386-402, (1997).

Isralewitz B., Izrailev S., and Schulten K., "Binding pathway of retinal to bacterio-opsin: a prediction by molecular dynamics simulations" *Biophys. J.* **73**, 2972-2979, (1997).

Izrailev S., Stepaniants S., Balsera M., et al., "Molecular dynamics study of unbinding of the avidin-biotin complex" *Biophys. J.* **72**, 1568-1581, (1997).

Izrailev S., Stepaniants S., Isralewitz B., Kosztin D., Lu H., Molnar F., Wriggers W., and Schulten K., "Steered Molecular Dynamics" in Algorithms for Macromolecular Modeling, (Springer Verlag) 1998, in press.

Klimasauskas S., Szyperski T., Serva S., et al., "Dynamic modes of the flipped-out cytosine during HhaI methyltransferase-DNA interactions in solution" *Embo J.* **17**, 317-324, (1998).

Koepke J., Hu X., Muenke C., Schulten K., and Michel H., "The Crystal Structure of the Light Harvesting Complex II (B800-850) from *Rhodospirillum molischianum*" *Structure* **4**, 581-597, (1996).

Kosztin D., Bishop T.C., Schulten K., "Binding of the estrogen receptor to DNA. The role of waters" *Biophys. J.* **73**, 557-570, (1997).

Lam W.C., Van der Schans E.J.C., Joyce C.M., Millar D.P., "Effects of mutations on the partitioning of DNA substrates between the polymerase and 3 '-5 'exonuclease sites of DNA polymerase I (Klenow fragment)" *Biochemistry-US* **37**, 1513-1522, (1998).

Merritt E.A., Bacon D.J., "Raster3D: Photorealistic molecular graphics" *Method Enzymol.* **277**, 505-524, (1997).

Phillips J.C., Wriggers W., Li Z.G., et al., "Predicting the structure of apolipoprotein A-1 in reconstituted high-density lipoprotein disks" *Biophys. J.* **73**, 2337-2346, (1997).

Ritz T., Hu X., Damjanovic A., and Schulten K., "Excitons and Excitation Transfer in the Photosynthetic Unit of Purple Bacteria" *J. Luminescence* **76-77**, 310-321 (1998).

Sabelko J., Ervin J., Gruebele M., "Cold-denatured ensemble of apomyoglobin: Implications for the early steps of folding" *J. Phys. Chem.* **102B**, 1806-1819, (1998).

Sharma R., Pavlovic V.I., Huang T.S., Lo Z., Chu S., Zhao Y., Zeller M., Phillips J., and Schulten K., "Speech/gesture interface to a visual computing environment for molecular biologists." IEEE Computer Graphics and Applications (accepted for publication).

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Wriggers W., Schulten K., "Stability and dynamics of G-actin: Back-door water diffusion and behavior of a subdomain 3/4 loop" *Biophys. J.* **73**, 624-639, (1997).

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Zeller M., Phillips J.C., Dalke A., Humphrey W., Schulten K., Sharma R., Huang T.S., Pavlovic V.I., Zhao Y., Lo Z., Chu S., "A visual computing environment for very large scale biomolecular modeling" in Proceedings of the IEEE International Conference on Application-specific Systems, Architectures and Processors (ASAP), p3-12, (IEEE Computer Society Press), 1997.

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Ai Z. and T. Frohlich, "Molecular Dynamics Simulation in Virtual Environments," EUROGRAPHICS 98, Lisbon, Portugal, Sept. 1998.

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Zeller M., Phillips J.C., Dalke A., Humphrey W., Schulten K., Sharma R., Huang T.S., Pavlovic V.I., Zhao Y., Lo Z., Chu S., "A visual computing environment for very large scale biomolecular modeling" in Proceedings of the IEEE International Conference on Application-specific Systems, Architectures and Processors (ASAP), p3-12, (IEEE Computer Society Press), 1997.

General Services

The 3D projection facility has been used for scientific, dissemination and training purposes. The facility is regularly included on UIUC tours by federal and state officials, and is operated by the Resource personnel, with demonstrations being made several times a week. Visitors to the facility over the past grant period included Dr. J. Palmer, University of Minnesota; Dr. T. Kazic, program officer, NSF; D. Searls, Vice President, Smith-Kline Beecham Pharmaceuticals; Prof. J. Katzenellenbogen, Dept. of Chemistry, UIUC; Prof. W. Gilbert , Harvard; Dr. J. Che, Dept. of Chemistry and Biochemistry, UCSD; L. Norris, Northwestern University; Four senior

undergraduates, Pohang University of Science and Technology in Korea; Dr. A. Garcia, Los Alamos National Lab; Dr. D. Bashford, Department of Molecular Biology, Scripps Research Institute; Prof. S. White, Dept. of Physiology & Biophysics, University of California at Irvine; Prof. A. Tropsha, School of Pharmacy, University of North Carolina C-H; Prof. W. Olson, Dept. of Chemistry, Rutgers Univ.; Dr. A. Wolffe, NIH; Prof. H. Scheraga, Baker Laboratory of Chemistry, Cornell University; Prof. R. Bruinsma, Dept. of Physics, UCLA; Prof. D. Beveridge, Wesleyan U; M. Gordon, prospective graduate student; Prof. D. Hofstadter, Indiana University, Bloomington; Dr. B. Saam, Washington U, S.L.; Dr. H. Luecke, Molecular Biology and Biochemistry, Physiology & Biophysics, University of California, Irvine; Dr. H. Roder, Fox Chase Cancer Center; Prospective Biophysics Student.; Prof. E. Hammeren, Dept. of Physics, University of Jyvaskula, Finland; Prof. V. Sundström, Chemical Physics, Lund University; Dr. A. Maeda, Department of Biophysics, Faculty of Science Kyoto University; H. Gunther, Assoc. Director, School of Chemical Sciences, UIUC; Prof. J. Fernandez, Department of Physiology and Biophysics, Mayo Foundation; Prof. A. Oberhauser, Mayo Clinic; Prof. J. Kuryan, Rockefeller University; Prof. F. Arnold, Center for Molecular Research, University of Chicago; Prof. Steve Benner, U of Florida; Prof. M. Colvin, Biology and Biochemistry Program, LLNL; Prof. W. Lubitz, Berlin Technical University.

The Resource organized an internal retreat for all the regular Resource members (March 13-14 1998) at Allerton Park, just outside of Champaign Urbana (Appendix II). The meetings offered an ideal setting and a relaxed atmosphere for deep discussions and the exchange of ideas between the members. The retreat costs were covered by a non-NIH source.

Our HTTP server is regularly maintained to give all users of the Internet access to publications, images, and routine activities of the Resource. The average number of unique host accesses per month is about 1,500. The address for our home page is *http://www.ks.uiuc.edu/*.

The Resource has again organized a popular seminar series in theoretical biophysics with the support of the Beckman Institute and NIH Resource funds. During the past year the following outside speakers have presented lectures in the Resource seminar series at the Beckman Institute:

Jian-wei Che, Department of Chemistry and Biochemistry UCSD, June 9, 1997; Lecture: *Quantum Control and Detection*

Alok K. Mitra, Department of Cell Biology, The Scripps Research Institute, La Jolla, CA, June 10, 1997; Lecture: *Three-dimensional Organization of a Human Water Channel*

Christof Schuette, Konrad-Zuse-Zentrum, Freie University of Berlin, Germany, July 7, 1997; Lecture: *Large Nonadiabatic Effects in Quantum-Classical Molecular Dynamics*

Angel Garcia, Los Alamos National Laboratories, Los Alamos, NM, September 15, 1997; Lecture: *Theoretical Description of Biomolecular Hydration - A Potential of Mean Force Approach*

Sascha Hilgenfeldt, AG Statistische Physik, Universitaet Marburg, Germany, September 16, 1997; Lecture: *Analysis of Rayleigh-Plesset Dynamics for Sonoluminescing Bubbles*

Michal Ben-Nun, Department of Chemistry, University of Illinois at UC, September 18, 1997; Lecture: *Multi-Electronic States Dynamics: Methodology and Applications to Dynamical Stereochemistry*

Donald Bashford, Department of Molecular Biology, Scripps Research Institute, La Jolla, CA, September 22, 1997; Lecture: *Development Applications of Macroscopic Models of Protein Electrostatics*

Alex Tropsha, School of Pharmacy, University of North Carolina, Chapel Hill, NC, October 13, 1997; Lecture: *Analysis and Prediction of Protein Structure Based on Delaunay Tessellation*

Wilma K. Olson, Department of Chemistry, Rutgers, The State University of New Jersey, New Brunswick, NJ, October 20, 1997; Lecture: *DNA Sequence and Three-Dimensional Structure*

Ehud Landau, University of Basel, Switzerland, October 21, 1997; Lecture: *Crystallization and Structural Determination of Bacteriorhodopsin in Lipidic Cubic Phases Towards Elucidating the Proton Translocation Pathway*

Harold A. Scheraga, Cornell University, Ithaca, NY, October 27, 1997; Lecture: *Theoretical Aspects of Protein Folding*

Robijn Bruinsma, University of California at Los Angeles, November 3, 1997; Lecture: *Electrostatic Interactions and DNA Condensation*

D. L. Beveridge, Department of Chemistry, Wesleyan University, Middletown, CT, November 10, 1997; Lecture: *Molecular Dynamics of Oligonucleotides with Phased A-tracts: Dynamical Models of DNA Bending*

Akio Maeda, Department of Biophysics, Kyoto University, Japan, November 19, 1997; Lecture: *FTIR Studies on the Photoactivating Process in Bacteriorhodopsin and Bovine Rhodopsin*

William F. Humphrey, Advanced Computing Laboratory, Los Alamos National Laboratory, Los Alamos, NM, January 20, 1998; Lecture: *Object-oriented Scientific Application Development Using the POOMA Framework*

James M. Lisy, Department of Chemistry, University of Illinois at U-C, Urbana, IL, February 2, 1998; Lecture: *Competition Between Non-Covalent Forces: The Influence of Ion-Molecule and Hydrogen-Bond Interactions*

George Pack, University of Illinois College of Medicine at Rockford, Rockford, IL, February 9, 1998; Lecture: *Computational Approaches to DNA Electrostatics*

Brian Saam, Department of Physics, Washington University, St. Louis, MO, February 16, 1998; Lecture: *Lung Imaging with Hyperpolarized Noble Gases: Diffusion Effects and Dynamic Ventilatory Function*

Christopher Jarzynski, Los Alamos National Laboratories, Los Alamos, NM, February 19, 1998; Lecture: *Irreversible Work and Equilibrium Free Energy Differences*

Hartmut Luecke, University of California - Irvine, CA, March 2, 1998; Lecture: *The Annexin XII Hexamer: does it insert into phospholipid bilayers?*

Villy Sundström, Chemical Center, Lund University, Lund, Sweden, March 11, 1998; Lecture: *Excitation Transfer and Interactions in Photosynthetic Light-harvesting*

Michael Colvin, Biology and Biotechnology Research Program, Lawrence Livermore Labs, Livermore, CA, March 16, 1998; Lecture: *Advanced Computational Chemistry for Biomedical Applications*

Julio M. Fernandez, Department of Physiology and Biophysics, Mayo Clinic, Rochester, MN, April 13, 1998; Lecture: *Recording of Folding/Unfolding Reactions in Single Proteins by AFM Techniques*

Alok Mitra, The Scripps Research Institute, La Jolla, CA, April 16, 1998; Lecture: *Three-dimensional Organization of Human Aquaporin Water Channel Revealed by Electron Crystallography*

John Kuriyan, The Rockefeller University, New York, NY, April 27, 1998; Lecture: *Structural Aspects of Growth Factor Signaling*

Steve A. Benner, Department of Chemistry, University of Florida, Gainesville, FL, April 30, 1998; Lecture: Evolutionary Analysis of Protein Conformation. Can the Prediction Problem be solved?

Training

As in previous years the training activities at the Resource greatly overlap with the service and dissemination efforts. In addition to the information provided in the previous service and dissemination sections, the Resource's Principal Investigators advise graduate students in their respective departments and offer rotation opportunities to undergraduates.

The Resource organized several events that are reported in the service and dissemination sections.

The Resource's projection facility was frequently used for Physics, Biophysics and Chemistry classes.

Long and short term visitors to the Resource, previously mentioned in the service section, benefited from on-the-job training and hands-on experience with the software developed at the Resource. The direct and intensive interactions with the software developers and the application

scientists, already familiar with the various features, made their stay at the Resource particularly advantageous.

The Resource maintains a small, yet well stocked library. We presently subscribe to 16 periodicals which include titles such as: Current Opinion in Structural Biology, Nature, Nature Structural Biology, Science, and Issues in Science and Technology. During the past year newly published books were purchased in areas such as quantum mechanics, human genetics, mathematics, biocomputing, protein folding, protein structure, parallel programming, system administration, and neurobiology. We expect to continue to purchase books, to keep our journal subscriptions, and possibly to add new ones, depending on our research needs and availability of funds. The Resource library is well cataloged. The catalog is available for Resource members on the web (*http://www.ks.uiuc.edu/Group/Library/*), and has become an important training tool for staff members and visitors.

Much of the research and development efforts at the Resource are carried out by graduate students. The list below includes Ph.D. recipients, postdoctoral associates, visitors and undergraduates who received their training at the resource during the past year:

Ph.D. Students

1. Willy Wriggers, Physics "Structure, Function, and Dynamics of Cell Motility Proteins" October 1997; Postdoctoral Associate, University of California at San Diego
2. Michael Zeller, Physics "Topology Representing Neural Networks in Robotics: Adaptive visu-motor control and intelligent path planning" January, 1998; Postdoctoral Research Associate, University of Southern California, Los Angeles, CA

Postdoctoral Associates

1. Sergey Stepaniants (1995–1997) Research Scientist, Rosetta Inpharmatics, Kirkland, WA
2. Xiche Hu (1994-1998) Assistant Professor, University of Ohio, Toledo, OH.

Visitors

1. Andre Krammer, August 1997 and March 1998, University of Washington, Seattle, WA
2. David Hurwitz, February 1998, University of North Carolina at Chapel Hill, NC
3. Zhirong Sun, Spring 1998, Qing Hua University, Beijing, China

Undergraduate Trainees

1. Arvind Sekar, University of Illinois, Computer Science (Summer 1997)

2. Jennifer Phend, Physics NSF/REU student (Summer 1997)
3. David Kaufman, Physics NSF/REU student (Summer 1997)
4. Nicholas Paul Dietz, University of Illinois, Computer Science (10/97–)
5. Justin Wozniak University of Illinois, Computer Science (3/98–)

Grant Number: P41RR05969
Report PD: (8/01/97-7/31/98)

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Grant Number: P41RR05969
Report PD: (8/01/97-7/31/98)