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PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

NATIONAL CENTER FOR RESEARCH RESOURCES
BIOMEDICAL TECHNOLOGY AREA

ANNUAL PROGRESS REPORT (8/1/98-7/31/99)

NIH RESOURCE FOR MACROMOLECULAR MODELING & BIOINFORMATICS

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Contents

This report describes research, development and service activities in 1998-99 at the National Institutes of Health funded Resource for Macromolecular Modeling and Bioinformatics. The report covers the 9th funded year of the Resource. This is the second year of a five-year funding cycle awarded to the Resource.

The Resource has advanced its computational tools for studying molecular biology of cells in several significant ways and has demonstrated the new potential of its software and methods on a broad spectrum of biomedical applications. The Resource has increased its user base further and it continues to be engaged in exciting collaborative projects.

The most important developments during the past year are: the establishment of the steered molecular dynamics method as a tool to investigate mechanical and adhesive properties of proteins relevant for many biological functions; near completion of a Windows version of VMD bringing high end molecular graphics to commodity workstations; completion of NAMD2 permitting effective, readily modifiable, and state-of-the-art molecular modeling on massively parallel machines; and initiation of the development of a software suite for network-based collaborations in structural biology.

As in the past the Resource focused its efforts on the following general goals

- Developing software to model and view ever-larger biomolecular units.
- Formulating theoretical concepts applicable to large aggregates.
- Developing software for mechanical manipulation of biopolymers, for probing adhesive interactions and molecular recognition, and for interactive modeling.
- 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.
- Broadening the scope of our software development to include network-based collaborative tools.
- Exploring cost effective computer platforms and maintaining a state-of-the-art computational laboratory.
- Engaging in demanding and relevant collaborations.
- Initiating service, training and dissemination activities.

The Resource is actively involved in extending the frontiers of biomolecular modeling beyond classical mechanics and classical force fields. With new dynamical methods, we have shown that the quantum mechanical effects associated with photochemistry and photophysics, i.e. multi-electronic state dynamics, can be incorporated into large-scale biomolecular dynamics. Ongoing work to establish a well-defined NAMD API will allow the incorporation of these new dynamical methods into the distributed versions of NAMD. These new techniques are being used to study the photodynamics of bacteriorhodopsin, which is closely related to the visual pigments, and in the future will see application to simulations of the radiation damage and repair in DNA that is directly relevant to certain forms of skin cancer. We have extended these methods to include also quantum mechanical effects associated with tunneling, which is of special interest in the context of proton transfer. The accuracy of the tunneling extensions has been demonstrated for small molecules, and we are currently working to show that they remain feasible for large protein molecules. Our fundamental investigations into the coupling of quantum chemistry and classical force fields are leading to promising new methods which will allow accurate treatment

of intermolecular forces involving electronically excited chromophores and/or metals in varying redox states. We have shown how short-range repulsion effects between classical force fields and quantum chemical subsystems may be accurately treated for small molecules and have also made inroads in the inclusion of charge transfer between classical and quantum chemical subsystems which will be crucial in simulating redox enzymes. Currently we are focusing on assessing the accuracy of these approaches and once this is established they will be incorporated into NAMD, allowing a new generation of mixed quantum-classical force fields.

The Resource from the outset considered its graphics and modeling software as a unit that should work together permitting graphical monitoring of modeling runs and graphical analysis of modeling trajectories. A further goal had always been interactive modeling involving the steering of molecular models and stretching and unfolding of proteins, docking and unbinding of ligands and other interactive investigations of adhesive forces crucial for self-assembly and maintenance of all cellular structures. Achieving this goal depended on advances in computing technologies that permit sufficiently fast simulations at teraflop speed. Such speeds are feasible today and the Resource has focused much of its efforts on developing steered and interactive molecular modeling as well as demonstrating its potential through pilot projects. For this purpose the Resource has added a so-called haptic input and output device to its graphics program that permits mechanical interaction with models. The Resource has also taken first steps for quantitative analysis of steered/interactive simulations introducing time series methods for the evaluation of potentials of mean force.

Several applications described below document already the power of the steered molecular dynamics methods. In a collaboration with atomic force microscopists, simulations explained a series of fascinating observations of so-called mechanical proteins, like the muscle protein titin and its ubiquitous relatives. Steered molecular dynamics also shed light on the maturation of antibodies, on the reaction kinetics of prostaglandin synthetase 1, 2, the targets for superaspirin, on binding and unbinding of ligands controlling nuclear hormone receptors which are involved in a wide class of diseases and involved, e.g., in hormone replacement therapy, and finally in understanding a key bioenergetic reaction in mitochondria, a bifurcated redox reaction apparently involving a large scale protein domain motion.

Teraflop computing is presently available only at few DOE operated national laboratories in the US, not to NIH funded researchers at academic institutions. The Resource organized in March 1999 a conference, “Opportunities in Molecular Biomedicine in the Era of Teraflop Computing,” in which the leaders in the field of molecular modeling provided compelling examples of biomedical research that could benefit from a hundred-fold increase in computer power. The participants aimed their arguments and discussions at NIH, hoping to persuade its leadership to make teraflop computing available to the biomedical community.

Researchers at the Resource were involved in collaborative projects that supported experimental groups, complementing their observations. The projects were characterized by a common need to carry out large scale or technically demanding simulations as well as requiring advanced computational tools. One such project investigated the role of water in mediating the recognition of DNA sequences by transcription factors. For this purpose a benchmark simulation of hydration patterns around DNA and a certain DNA analogue that controls water binding were investigated to guide future experimental work. The Resource continued a fruitful collaboration on high-density lipoproteins that play a well-known role in lipid and cholesterol metabolism. The

work focused on characterizing the structure of complexes of lipids with apoliproprotein A1 and a new round of state-of-the-art simulations has been initiated. The decade long collaborations on bacteriorhodopsin at the Resource have reached an exciting and critical phase with the availability of much improved crystallographic structures. All crystallographic groups collaborate with the Resource, which has become a clearinghouse for the evaluation of the available structures and for attempts to relate the structures to primary photoprocesses in the proteins and to proton transport by means of internal water.

The Resource is also playing a key role in the investigations of light harvesting proteins in photosynthesis – even though not of direct medical relevance, the light harvesting proteins provide in a nutshell a laboratory for understanding the quantum mechanical nature of protein function in general and, of great biomedical implication, for an understanding of the self-assembly of multi-protein systems. Lastly, the Resource began a collaboration on a role of cryptochromes in the visual pathway and the pineal as magnetosensitive receptors of light; based on earlier work at the Resource on magnetic field sensitive biochemical reactions in bacterial photosynthesis researchers study the magnetic field dependence of a radical pair reaction in photolyases, enzymes that are closely related to cryptochromes.

The Resource has obtained first results in its new area of bioinformatics. Focusing on the development of a phylogenetic analysis of metabolic pathways, a first study of a number of pathways has been completed. In regard to its primary mission of method development the Resource can also claim a very successful year. First, the port of its molecular graphics program VMD to the Windows environment has been nearly completed – a first release is already available. This port required a complete revision of the VMD package involving a multi-year programming effort. The Resource placed great emphasis on this development since it forecasted (correctly) that sufficiently powerful engines that are a prerequisite for advanced molecular graphics are rapidly becoming a commodity in connection with modern personal computers. This development will permit a broad range of biomedical researchers to take better advantage of structural information in their research by permitting rendering and analysis of structures from the various databases. In fact, one such database, the Cambridge crystallographic database, will make the new Windows version of VMD its standard molecular graphics access tool.

The Resource's modeling program NAMD has undergone a new development cycle culminating in a new version, NAMD2. The program with the most advanced modeling features available today, e.g., NpT ensemble simulations and periodic boundary conditions with full electrostatics, has been redesigned for effective execution on massively parallel computers. In fact, the program runs with unsurpassed effectiveness on more than 200 processors, demonstrating its suitability for the teraflop computing era. While adding features and realizing sophisticated message passing and load balancing schemes the program improved its usability by researchers who seek to alter the code for their own needs. The Resource has also improved algorithmic and conceptual approaches to large-scale simulations. The development of better integration schemes that promise a speed-up by a factor of ten over conventional algorithms is one such effort. The use of elastic rod models to simulate segments of DNA larger than ten base pairs, is another such effort. In the latter case the Resource expects to model soon the complete nucleosome and even multi-nucleosome systems, providing an improved basis for the understanding of the storage and expression of DNA in the cell's nucleus.

The Resource also had an opportunity to consolidate its numerical laboratory through key acquisitions. A symmetric, fault tolerant, file server system has been installed that serves over 500 GB of project data through 100 Mb fully switched Ethernet to over 100 computer systems. A Beowulf cluster of sixteen dual PentiumII-400 MHz processors with 256 MB per node serve as a main computer platform for large scale modeling. A server cluster of four Dec Alpha 21264-500MHz provides an extremely fast computing platform to carry out long time simulations and simulations combined with quantum chemical calculations of force fields. Many of the desktop systems have been upgraded as well so that the computational facilities of the Resource presently are completely overhauled and state-of-the-art.

The Resource's service, training and dissemination areas experienced a highly productive and dynamic year as is evident from the various activities to be reported here. The services offered by the Resource are enjoyed by a vast number of biomedical researchers, domestic and international. A large fraction of our user population is directly involved with medical research sponsored by National Institutes of Health (NIH). An estimated 20% of our software (VMD and NAMD) users are NIH supported. The meeting Opportunities in Molecular Biomedicine in the Era of Teraflop Computing, organized by the Resource on March 3-4 of this year, brought together world-class biomedical researchers, most of whom supported by NIH. Moreover, the recent NIH Collaboratory supplement awarded to us will further strengthen our resolve to offer quality service to the structural biology community. It will also enhance our capabilities to create and sustain a broader spectrum of services.

With the collaboratory initiative and intensive recruiting efforts, we substantially increased the size of our technical support staff. By this summer we will have established a cohesive and dedicated team of 5 highly qualified programmers ready to fully attain our software development aspirations. A highly skilled system administrator has recently joined the Resource and will ensure the professional support of the cutting end technology needed to meet our research and development targets.

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Evolution of Metabolism

The accessibility of numerous completely sequenced genomes as phylogenetic diverse representatives of all three known domains (archaea, bacteria, and eukaryotes) has dramatic effects on the strategy of analyzing these genomes. Complete genomes permit a representation of higher-level functional components per organism, as demonstrated by Overbeek et al.[1], but still a need exists for methods to compare higher-level functional components such as metabolic networks between (and within) organisms.

We suggested a synthesis between representation and comparison of complete metabolic networks and individual enzymes and substrates.* An information system suitable for this task has been outlined and found in the WIT-system. A method for calculating distances between metabolic networks based on sequence-information of the involved biomolecules has been presented and extended to permit a comparison to other similar networks with missing functional roles (substrates and enzymes)[2,3]. Distances between individual functional roles were obtained by multiple sequence analysis. These individual distances were then used to calculate an overall distance matrix reflecting the global distance (Figure 1). In case of pathways with missing functional roles gap penalties were introduced. With the global distance matrix a phylogenetic reconstruction is performed.

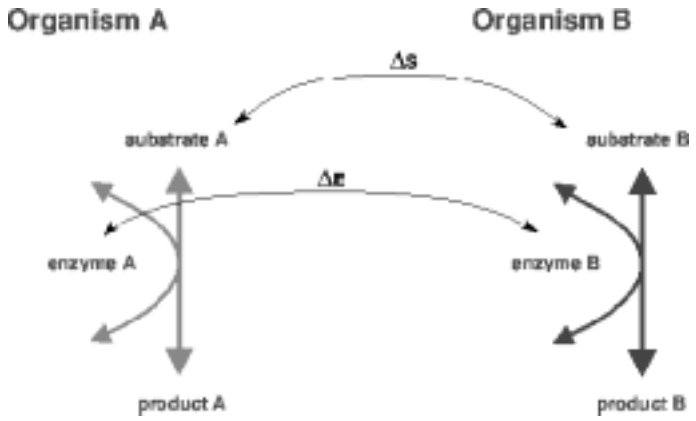

Figure 1: Distance between two pathways. Individual distances ΔE, ΔS between sequences of the same functional role are used to calculate a global distance Δ.

To illustrate the method, four electron transport pathways have been analyzed: (1) the ferredoxin – NADPH reductase pathway; (2) pathways utilizing ferredoxin; (3) the malate – aspartate shuttle; (4) terminal oxidase complexes. The analysis reveals a close relationship between pathways of organisms within the same genus. According to Woese[4], metabolic genes are among the most modular in the cell, and their genes are expected to travel laterally, even today. Such adaptations of single genes as well as horizontal transfer of complete pathways between organisms are confirmed by our phylogenetic analysis.

The analysis of the evolution of terminal oxidases (quinol oxidase as well as cytochrome *c* oxidase) and the comparison with a study performed by Musser and Chan[5] served as a test for the method. To accomplish a phylogenetic analysis of terminal oxidase, a hypothetical cytochrome *c* oxidase pathway with six functional roles has been constructed. The corresponding

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

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functional roles are: cytochrome *c* oxidase polypeptide I to IV (1)-(4); bc_1 complex or its homologues, cytochrome bo_3 or quinol oxidase (5); and the Rieske protein (6). The remaining polypeptides V to VIII for cytochrome *c* have not been considered because sequences which code for these polypeptides have only been found in *S. cerevisiae*.

Figure 2 shows the phylogeny for the cytochrome *c* oxidase and quinol oxidase complexes. A cut between cytochrome bo_3 ubiquinol oxidase complexes (cytBO) and simple quinol ba_3 oxidase (qox) complexes on the one hand and cytochrome bc_1/cytochrome *c*/cytochrome *c* oxidase supercomplexes, cytochrome caa_3 complexes, mitochondrial cytochrome bc_1/cytochrome aa_3 (cytochrome *c* oxidase) complexes, and aa_3 type quinol oxidase complexes on the other hand can be noticed (Figure 2). A close relationship of cytochrome bo_3 between *E. coli*, *P. aeruginosa*, *Y. pestis* and *B. subtilis* can be noticed (left part of Figure 2). All four organisms utilize the cytochrome bo_3 complex as terminal oxidase.

Similar to the analysis of Musser and Chan[5], a progression from simple cytochrome *c* complexes (*S. acidocaldarius*) via *Mycobacteriaceae*, *Synechocystis*, *A. aeolicus* and *P. aeruginosa* to the complete set of the cytochrome caa_3 complex of *B. subtilis* and the mitochondrial cytochrome bc_1 and cytochrome aa_3 (cytochrome *c* oxidase) complexes of *S. cerevisiae* and *C. elegans* is observed. Musser and Chan conclude that the common ancestor of cytochrome bc_1/cytochrome *c* oxidase complexes was a quinol oxidase complex. Figure 2 emphasizes the suggested evolutionary path from quinol terminal oxidase complexes and cytochrome bo_3 ubiquinol oxidase complexes to mitochondrial cytochrome bc_1/cytochrome *c* oxidase complexes. Thus, even with functional roles missing in the pathway of terminal oxidation, the presented method constructs a phylogeny of quinol and cytochrome oxidase complexes in good agreement with the results by Musser and Chan.

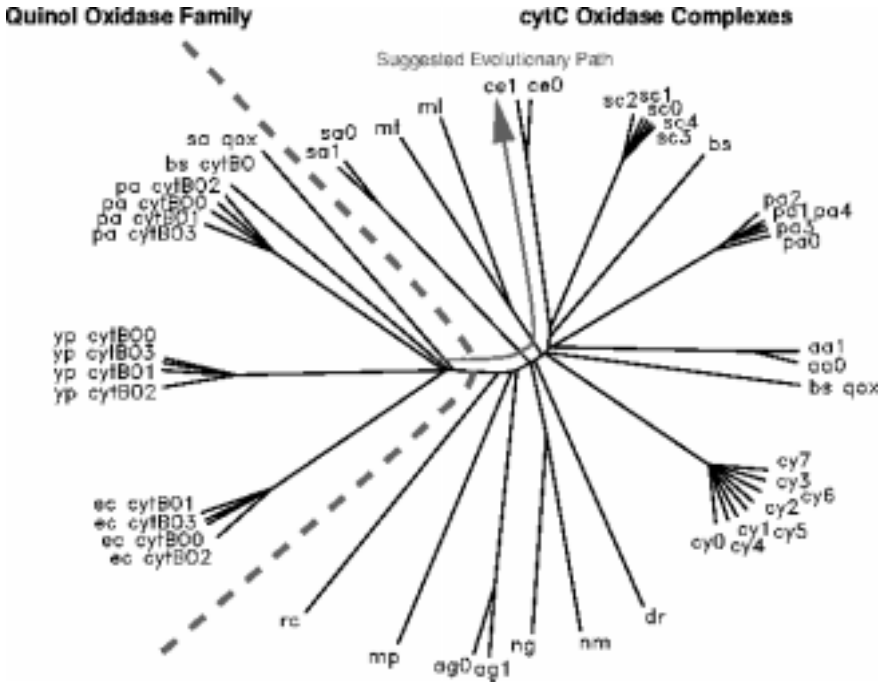

Figure 2: Cytochrome *c* oxidase complexes. The phylogenetic relationship of cytochrome *c* and quinol oxidase complexes is depicted. The thick dashed line indicates the split between quinol oxidase and cytochrome *c* oxidase complexes. The solid line denotes a suggested evolutionary path (see text).

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Steered Molecular Dynamics Simulations of Force-Induced Protein Domain Unfolding

The architecture of immunoglobulin-like (Ig) and fibronectin type III-like (Fn-III) domains constitutes possibly the most prevalent structural motif of proteins. These proteins serve numerous roles in cell-cell signaling, cell-cell aggregation, embryogenesis, as well as in mechanically coordinating and strengthening cells and tissues. The proteins are implicated in the etiology of many diseases, ranging from heart insufficiency to cancer. Recently, atomic force microscopy (AFM) experiments[6,7] have investigated the mechanical properties of connected Ig and Fn-III domains. We have simulated these experiments to explain the specific mechanical properties of these proteins.[*] The research employed the steered molecular dynamics (SMD) technique[8], developed at the Resource, that permits researchers to mechanically manipulate models of proteins. The technology is based on the Resource software which combines its high-end graphics tool VMD[9] with its simulation program for parallel computers NAMD[10,11].

With SMD we described of the response of the titin immunoglobulin domain I27 at the onset of domain unfolding in quantitative agreement with AFM observations. We show that if forces stronger than 50 pN are applied to the terminal ends the two hydrogen bonds between the antiparallel A and B β-strands break with a concomitant 6-7Å elongation of the protein. If forces strong enough to unfold the domain are applied, the protein is halted in this initial extension until the set of all six hydrogen bonds connecting strands A' and G break simultaneously. This behavior is accounted for by a barrier separating folded and unfolded states, the shape of which is consistent with AFM and chemical denaturation data. We also demonstrate that steered molecular dynamics simulations which induce unfolding through slow pulling (speed 0.1 Å/ps) predict unfolding forces that are within a factor of two with force values extrapolated from AFM observations[12,13].

The tenth type III module of fibronectin, $FnIII_{10}$, possesses a β-sandwich structure consisting of seven β-strands (A–G) that are arranged in two anti-parallel sheets[14]. It mediates cell adhesion to surfaces via its integrin binding[15] motif, Arg7, Gly79, and Asp80 (RGD), that is placed at the apex of the loop connecting β-strands F and G. SMD simulations in which tension was applied to the protein's terminal ends revealed that the β-strand G is the first to break away from the module upon forced unfolding, while the remaining fold maintains its structural integrity[16]. The separation of strand G from the remaining fold resulted in a gradual shortening of the distance between the apex of the RGD-containing loop and the module surface which potentially reduces the loop's accessibility to surface-bound integrins[17]. The shortening is followed by a straightening of the RGD-loop from a tight β-turn into a linear conformation which suggests a further decrease of affinity and selectivity to integrins. The RGD-loop is therefore strategically located to undergo strong conformational changes in the early stretching stages of the module, and thus constitutes a mechanosensitive control of integrin recognition.

SMD has also been applied to investigate the response of other protein domains to stretching apart of their terminal ends. The simulations mimic atomic force microscopy and optical tweezers experiments[6,7], but proceed on much shorter time scales. The simulations on 10 different domains for 0.6 nanoseconds each reveal two types of protein responses: the first type, arising in certain β-sandwich domains, exhibits nanosecond (ns) unfolding only after a force above 1500 pN is applied; the second type, arising in a wider class of protein domain structures,

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

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requires significantly weaker forces for ns unfolding. In the first case, strong forces are needed to concertedly break a set of inter-strand hydrogen bonds which protect the domains against unfolding through stretching; in the second case, stretching breaks backbone hydrogen bonds stabilizing the structure one by one, and does not require strong forces for this purpose (see Figure 3). This classification provides an explanation of why Ig and FnIII domains exist widely in the mechanical proteins which need to sustain stretching forces very often physiologically[18].

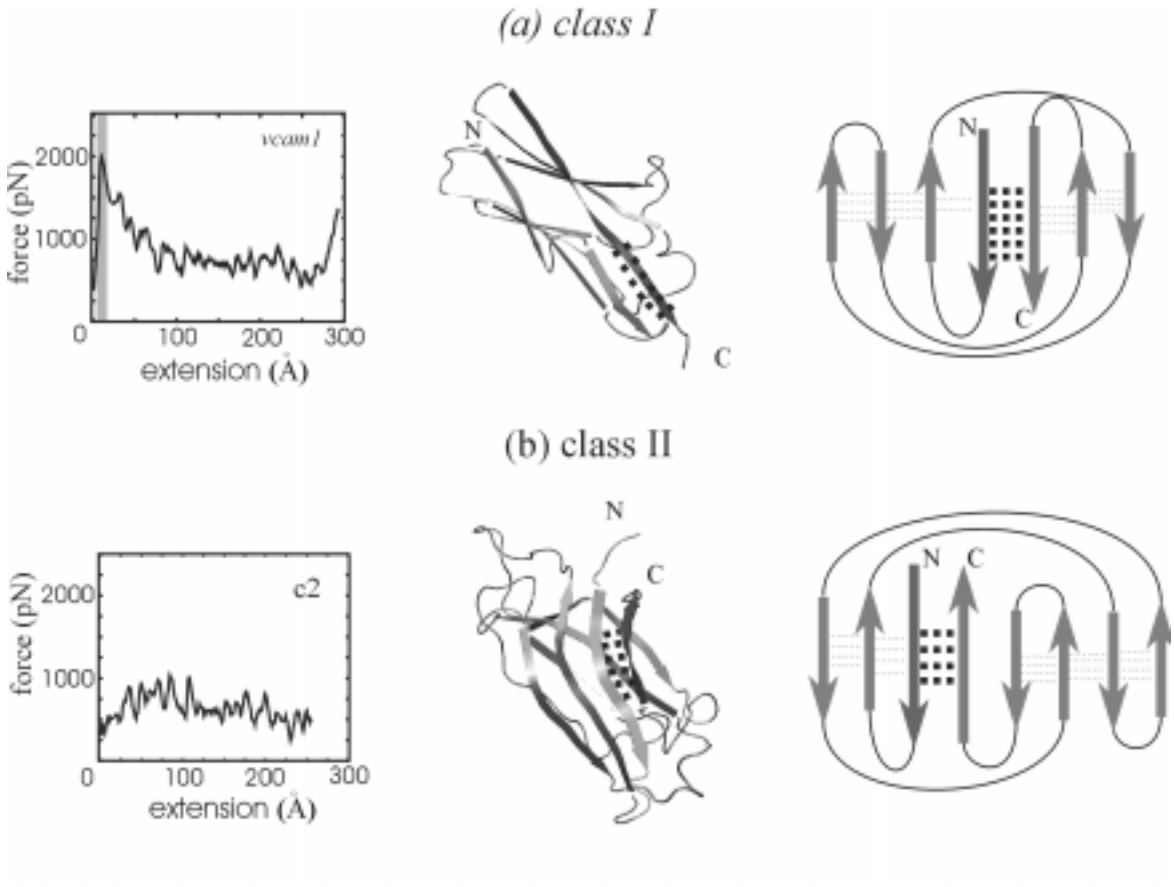

Figure 3: Force-extension profiles, domain structures and cartoon representation of protein backbones of two representative cases of protein domains under stretching. Dashed lines indicate inter-β-strand hydrogen bonds. (a) First domain of cell adhesion protein V-CAM, a class I domain. Stretching this domain with SMD reveals a dominant short-extension force peak at the force-extension profile (highlighted with gray box). (b) C2 domain of synaptotagmin, a class II domain. The force-extension profile of SMD simulation of stretching this domain showed no clear force peak. This figure suggests that class II domains unfold much more easily in response to stretching force than class I domains. This figure was created with VMD[9].

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Maturation of Antibody/Antigen Interactions

Catalytic antibodies are engineered molecules capable of performing chemical reactions on their antigen substrates. This unique ability makes these molecules excellent therapeutic candidates, since they will be able to catalyze clinically relevant chemical reactions within the cell. The understanding of their structure and function could lead to targeted development of drug molecules that may be used for example for cancer therapy or drug abuse[19]. The process of raising these catalytic antibodies is accomplished by first exposing the antibody to a specific antigen. The antibody then undergoes a maturation process that leads to the expression of a mature, mutated, antibody. This mature antibody exhibits an increased affinity for the antigen of several orders of magnitude, and thus an increased efficiency. Our goal is to understand at the molecular level how maturation leads to this increased efficiency.[*]

Figure 4: complex antibody (cartoon representation)/antigen (spheres). This figure was created with VMD[9].

Crystal structures of the catalytic antibody 48G7, wild type or mature, complexed with the antigen or unbound, were obtained recently by Wedemayer et al.[20], and a structure of the wild type antibody bound to the antigen is shown in Figure 4. Analysis of these crystal structures suggests that the mature antibody, which differs from the wild type by 9 mutations, is pre-adapted for the acquisition of its catalytic function. Whereas fixation of the antigen on the wild type antibody leads to significant structural rearrangements, fixation of the antigen on the mature antibody does not produce significant structural alterations. These experimental results suggest

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

that the mature antibody is more structurally rigid than the wild type form. Binding of the antigen on the mature protein operates through a “lock and key” mechanism. On the other hand, wild type antibodies having more conformational flexibility, bind antigen with an “induced fit” mechanism. This “conformational hypothesis” could explain differences in affinity between the wild type and mature forms of the protein.

Molecular dynamics simulations have been used to test changes in flexibility for various different antibodies[21,22]. These earlier works also suggested a possible change in flexibility upon mutation or unbinding of the antigen. However the accuracy of these models was limited by the absence of crystal structures for the unbound antibody or for its mature form. These limitations are now overcome by the recent availability of crystal structures for all of the above antibody states.

Our simulation study of the antibody-antigen complex used the CHARMM program[23]. Semi-empirical methods were employed to obtain parameters for the antigen, a nitrophenyl phosphonate transition-state. All four crystal structures were solvated with a 10Å shell of water. Molecular dynamics simulations of all crystal models were performed at room temperature for up to 450 ps. The rms fluctuations of the C alpha were recorded as a function of time. It was observed that during the initial stages of the simulations the wild type fluctuations were significantly higher when compared to that of the mutant antibody. However, we were concerned with these results since the antibody appeared distorted. We considered that these differences in fluctuations could be artifacts of the thin hydration shell. A test system using a larger spherical hydration shell was used on the wild type antibody and the simulation was repeated. This model preserved the antibody structure, but at a higher computational overhead.

Parallel to stability analysis by molecular dynamics simulations computational mutagenesis studies were performed. The influence on mutations on all four antibody structures were investigated by using a system based on knowledge-based potentials of mean force[24]. By using a fixed structure, point-mutations in the sequence were introduced and their influence on the energetics of the system sequence and structure were studied. The advantage in using knowledge-based potentials is the tremendous speed of such calculations. The mutagenesis analysis suggest a high sensitivity of the wild type unbound to the antigen on mutations. Only the heavy chain was destabilized even if mutations were introduced in the light chain. In contrast to the destabilization of the wild type bound structure, both mature structures as well as the wild type structure bound to the antigen exhibit tolerance against mutations. We conclude that the wild type unbound structure is highly flexible and adaptable to provide an environment for binding of a variety of antigens. The bound antigen provides a “scaffold” for an optimal antibody structure. Both mature structures have been stabilized by mutations to maintain optimal binding.

Our molecular dynamics study on these four antibodies will be re-run with the larger shell. Due to the large size of the molecular system (~160,000 atoms), we will use the program NAMD2[11], a highly parallel molecular dynamics program, in order to accelerate our calculations and obtain results in an reasonable time. Our models will be used in turn to study the non-equilibrium process of antigen unbinding. Steered Molecular Dynamics (SMD)[8] will be used to simulate the unbinding pathway of the ligand and monitor any structural changes that may occur upon unbinding. We feel that SMD can also provide insights into identifying residues on the antibody that are responsible the conformational differences observed between the wild and mutant crystal structures.

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Molecular Visualization: The Program VMD

VMD[9] is the molecular visualization component of the MDScope computational environment.* The program is designed to facilitate and advance biomedical research and to be useful to computer experts and non-experts alike. VMD provides interactive 3-D molecular visualization and analysis capabilities, an extensive scripting language, and the ability to read many molecular file formats. VMD 1.2 was released on August 1, 1998. VMD 1.3 was released on April 5, 1999. VMD 1.4 is currently under development.

The main goal for VMD this past funding period was to make it available to a much broader user community on a variety of affordable hardware, by developing a platform-neutral source code and by increasing overall performance and efficiency. Consequently,

1) more biomedical researchers can now visualize much more complex systems than while retaining high levels of interactive rendering performance;
2) molecular systems can be visualized on less powerful and more affordable computers.

Through the use of the OpenGL graphics library, VMD can now be used on a wider variety of computer systems than ever before. VMD can be run on most Unix systems, including AIX, IRIX, HP-UX, Linux, Solaris (both Sparc and x86), and Tru64 Unix. VMD 1.3 contains the first support code for non-Unix systems such as Microsoft Windows. The first Windows version of VMD will be released later this year, and is expected to more than double the VMD user population.

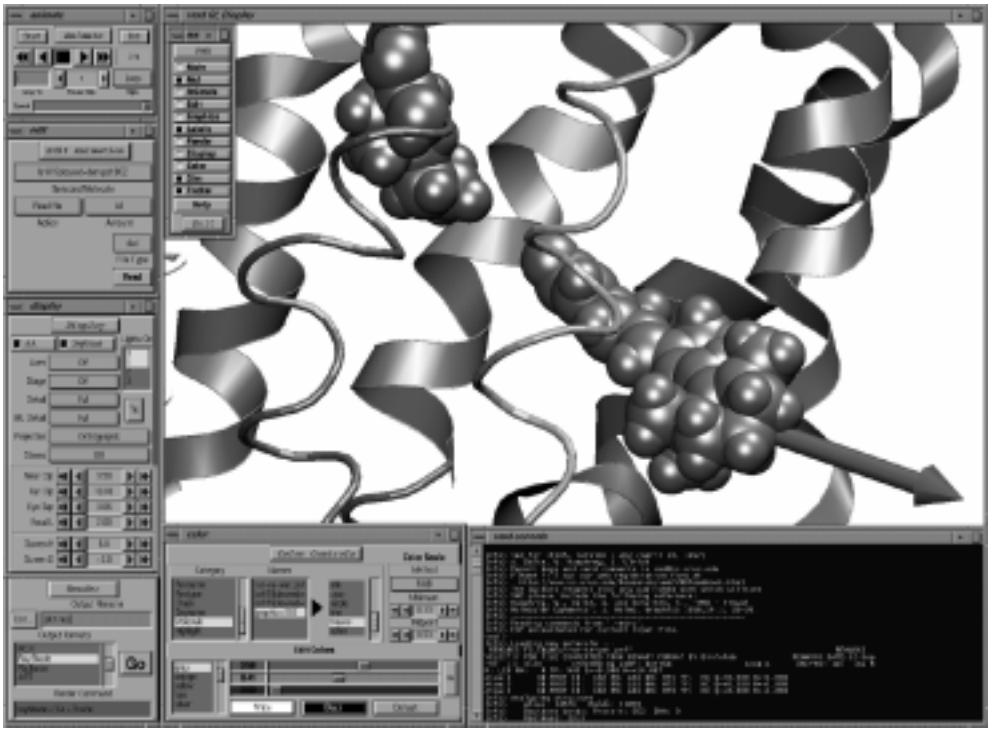

Figure 5: The VMD (Visual Molecular Dynamics) graphical user interface.

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

Efficiency improvements to VMD have targeted both “time” and “space”. The OpenGL versions of VMD 1.2 and 1.3 incorporate significant improvements in 3-D rendering performance. These improvements are the result of sophisticated rendering techniques which maximize the amount of computation delegated to the graphics accelerator hardware commonly found on modern PC’s and workstations. These improvements have resulted in a factor of five increase in the overall rendering speed of VMD. The performance of computers with limited or nonexistent 3-D graphics acceleration has been improved significantly through the elimination of unnecessary geometric computations. The use of geometry caching techniques has eliminated many repetitive computations by maximizing the reuse of highly tessellated geometric shapes. VMD 1.3 contains many efficiency improvements related to memory usage and traversal of data structures. Improvements to core VMD data structures yielded a 15% decrease in overall memory usage, which is a significant savings when working with large molecular systems consisting of 100,000 atoms or more.

VMD 1.4 will be the first release of VMD to support Microsoft Windows. The improvements to portability, rendering algorithms, and overall efficiency in VMD 1.2 and 1.3 have been essential steps in making VMD usable on personal computers. VMD 1.3 contains initial support for the FLTK graphical user interface toolkit, which will replace the XForms toolkit in future versions of VMD. The FLTK toolkit provides enhanced efficiency over XForms (currently used in VMD), supports Microsoft Windows, and is available in source code form.

Future VMD development will focus on enhancing user friendliness on all supported platforms. The 3-D rendering engine in VMD will be updated with new graphics algorithms which will improve the visual quality of many molecular representations while maintaining or exceeding current interactive rendering performance. Future work in improving the data structures and algorithms in VMD will help it scale up to visualize extremely complex molecular systems at the forefront of biomedical research.

An agreement about to be signed with the Cambridge Crystallographic Data Centre (CCDC) will establish VMD as the standard visualizer of the Cambridge Structural Database (CSD). CSD is CCDC’s primary product, offering the largest small-structure database in the world to the biomedical community. Similar agreements with other databases and publications are being explored.

For details on VMD’s user population and profile, registration and citations, please see the Service section on pp. 75.

BTA UNIT: T

TITLE: Computational Facility

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

AXIS I: 11

AXIS II:

INVEST1: Charles R. Brown

DEGREE1: B.S.

DEPT1: The Beckman Institute

NONHOST1:

% BRTP $: 6%

ABSTRACT: In the past year the computational facility has been upgraded to meet our increasing computational and visualization demands.* The group currently has 55 active users within the group and 35 outside users.

The computational power of the Resource has been vastly increased with the addition of a 32-processor Beowulf cluster, a quad-processor SGI Origin 200, and four dual-processor Alpha compute servers. The Beowulf cluster is the primary platform for NAMD development as well as for simulation jobs. The anticipated addition of a high-bandwidth interconnect will allow for continued development of the NAMD program[11] in new directions. The quad processor SGI Origin 200 is primarily used to run commercially available programs such as XPLOR, Gaussian, and the MSI suite of products, as well as our own internally developed MD package, NAMD. On the average, our computational machines are running at 65% of total capacity. Our plans for next year include an upgrade of our 3D visualization facility, the purchase of additional computational power, and new desktop workstations for the researchers and administration.

We have expanded our graphical power and capabilities with the addition of three new machines, an HP C200 workstation with FX4 graphics, an HP Kayak with FX6 graphics, and a Sun Ultra 2360 with Elite3Dm6 graphics. These machines, in addition to our SGI Onyx 2, take care of the bulk of our day-to-day visualization needs. The large amount of RAM, fast processors, and high performance 3D-graphics accelerators allow for the visualization of very large molecular systems.

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

We have upgraded our file and information servers to include two dual-processor Sun Enterprise 250 file servers with 250 GB of total storage and three Sun Ultra 5 systems providing a variety of network services. Our servers provide nearly a half-terabyte of data to over 100 workstations, backed up with two 80 GB Digital Linear Tape (DLT) auto-changers. In total, we have 435 GB of online storage available to researchers, up from only 130 GB a year ago.

Over the past year we have been evaluating hardware and software for Year 2000 compliance. To this end, we have been diligently upgrading, patching, or replacing these systems so the Resource will be fully functional after the year 2000. This has given us the opportunity to move many of our existing administrative applications (databases, calendars, systems accounting) from specific platforms to our web-based Intranet.

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 36,000 service units on NCSA's Origin2000 and 36,000 service units on SDSC's T3E.

Finally, the Beckman Institute has recently upgraded our networking from shared 10baseT Ethernet to fully switched 100baseT Ethernet. This has greatly increased the bandwidth available to the researchers' workstations.

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, 48

INVEST1: Robert Brunner

DEGREE1: B.S.

DEPT1: Department of Electrical and Computer Engineering

NONHOST1:

INVEST2: David Hardy

DEGREE2: M.S.

DEPT2: Department of Computer Science

NONHOST2:

INVEST3: Jim Phillips

DEGREE3: M.S.

DEPT3: Department of Physics

NONHOST3:

INVEST4: Krishnan Varadarajan

DEGREE4: M.S.

DEPT4: Department of Computer Science

NONHOST4:

% BRTP $: 6% (T), 10% (D)

ABSTRACT: NAMD, the simulation component of the MDScope modeling environment, continues to evolve as a production quality molecular dynamics tool

incorporating the latest in parallel computing, software development, and simulation methodologies.*

The past year has seen the conclusion of the NAMD 1.X[10] development cycle with the official release of version 1.5, incorporating bug fixes, software library updates, simplified installation, and performance improvements of up to 30%. NAMD 1.5 serves as a significant update to external users who have incorporated local modifications into the NAMD 1.X source code, which differs considerably from that of the substantially redesigned NAMD 2.0.

The stability and speed of NAMD 2.0[25,11,26] have been the foci of development during its extended beta testing period, which culminated in the first non-beta release in March 1999. Many bugs, which were exposed by large machines such as the Cray T3E and SGI Origin 2000, by slower networking on our local Linux cluster, and by long production runs, have been fixed. Improvements have also been made to the underlying Converse messaging system[27], which replaces PVM in NAMD 2.0.

Syntax changes that enhance the readability of messaging calls in NAMD are being incorporated into the source code, which is scheduled to be released as version 2.0.1 in May 1999. Finally, user-oriented features have been added including improved constant pressure simulation methods, CHARMM parameter format compatibility, and free energy of conformational change calculations.

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

BTA UNIT: T, D

TITLE: Molecular Visualization: The Program VMD

KEYWORDS: molecular graphics, interactive visualization

AXIS I: 9

AXIS II: 42

INVEST1: John E. Stone

DEGREE1: M.S.

DEPT2: The Beckman Institute

INVEST2: Justin Gullingsrud

DEGREE2: B.A.

DEPT2: Department of Physics

NONHOST2:

% BRTP $: 7.5% (T), 10% (D)

ABSTRACT: VMD is a sophisticated molecular visualization program developed at the Resource* to provide biomolecular display and analysis capabilities to biomedical researchers[9]. The primary development goals for VMD in the last year have been portability, efficiency, and correctness. The resulting increase in the number and variety of VMD users has provided VMD developers with much useful feedback, helping to eliminate software bugs and ensuring the relevance and quality of the software.

VMD 1.2 was released on August 1st, 1998 and included many functionality and efficiency improvements, most notable are:

- rendering speed improved by a factor of five for OpenGL hardware;
- support for new Unix platforms with OpenGL: AIX, Linux, Solaris, HP-UX;
- stereoscopic display support for OpenGL platforms;
- support for Tk graphics;
- support for MSMS molecular surfaces;
- support for GRASP file format.

VMD 1.3 was released on April 5th, 1999 and contains many significant improvements over VMD 1.2, most notably:

- decreased overall VMD memory usage by 15%;

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

- redesigned VMD snapshot feature for greater portability;
- updated with Mesa 3.0 and Tcl/Tk/TclX 8.0.4;
- added support for the Tachyon multiprocessor ray tracer;
- ported to Solaris x86 and IRIX 6.x.

Since the release of VMD 1.3 on April 5th, 1999, more than 700 users have registered and downloaded the program. Of the 700 registered VMD 1.3 users, close to 25% are NIH supported researchers.

Future VMD development will focus on enhancing user friendliness and additional performance enhancements. VMD 1.4, scheduled to be released in early Fall 1999, will be the first release of VMD to support Microsoft Windows.

BTA UNIT: T

TITLE: Algorithm Development

KEYWORDS: integration methods, multiple time stepping, molecular dynamics, Langevin dynamics

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 $: 3%

ABSTRACT: Typical molecular dynamics simulations compute atomic trajectories in time increments of length 1 fs with each step requiring a costly force evaluation. Speedups can be achieved by the use of multiple time stepping algorithms, which take time steps as long as 4 fs and do multiple evaluations of only the short-range forces.*

A further increase in the time step to 6 fs has been achieved in NAMD 1.5 using the mollified impulse method[28], which is based on incorporating averaging into the long-range forces. These and other algorithms for molecular dynamics are surveyed in [29,30].

A recently developed variant of the mollified method now allows a time step of 7 fs. The time step is limited by the occurrence of resonance-induced instabilities. It may be possible to design integrators that are more stable using analytical tools of [31]. Alternatively, the use of light Langevin damping with the mollified method permits time steps of 18 fs and possibly greater. Future work involves increasing the length of the longest time step, optimizing parameters, and implementation details.

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

BTA UNIT: T

TITLE: First Principles Studies of Tunneling Effects

KEYWORDS: proton transfer, semiclassical dynamics, quantum dynamics, *ab initio*, tunneling splitting

AXIS I: 2, 9

AXIS II: 74c

INVEST1: Michal Ben-Nun

DEGREE1: Ph.D.

DEPT1: The Beckman Institute and Department of Chemistry

NONHOST1:

% BRTP $: 4%

ABSTRACT: Proton transfer and coupled electron-proton transfer are important in many biochemical processes, for example, glycolysis and oxidative phosphorylation. There is therefore much interest in simulating such reactions. However, there are two main stumbling blocks in molecular modeling of proton transfer. The quantum mechanical nature of the nuclei must be confronted to include tunneling (and zero-point-energy) effects and at the same time the potential energy surface must be capable of describing bond rearrangement. The latter is often quite awkward in the context of analytical empirical functions and an attractive alternative is the use of *ab initio* dynamics, where the electronic Schrödinger equation is solved as needed, i.e. “on-the-fly”.

We have studied tunneling effects using a new *ab initio* semiclassical technique[32].* The semiclassical method solves the electronic Schrödinger equation simultaneously with the semiclassical tunneling dynamics[33,34], thereby allowing for chemical bond-rearrangement. Proceeding entirely from first-principles, we applied the method to the intramolecular proton transfer in malonaldehyde and found a calculated splitting of 21±1 cm^{-1}, in excellent agreement with the experimental value[35] of 21.6 cm^{-1}.

We have also shown that our *ab initio* real-time quantum dynamics method[36] can be applied successfully to treat tunneling effects[37]. The *ab initio* quantum method[37] is theoretically and computationally more challenging than the semiclassical one because both the nuclei and the electrons are treated quantum mechanically. To validate the method, we have

* URL: http://hobbes.scs.uiuc.edu/

used various model problems for which an exact numerical solution of the nuclear Schrödinger equation is possible. Quantitative agreement in expectation values, tunneling doublets and tunneling splitting was obtained for all the models at a relatively low computational cost. Therefore, we believe that hydrogen-bonded proton transfer systems can now be studied using *ab initio* quantum dynamics.

In the future, we plan to apply, and compare the results of, both methods to ground and excited state proton transfer and coupled electron-proton transfer processes.

BTA UNIT: T

TITLE: *Ab initio* Studies of Early Photoisomerization Dynamics in Polyenes

KEYWORDS: excited states, electronic quenching, conical intersections, pyramidalization, *cis-trans* isomerization, polyenes

AXIS I: 2, 9

AXIS II: 74a

INVEST1: Michal Ben-Nun

DEGREE1: Ph.D.

DEPT1: The Beckman Institute and Department of Chemistry

NONHOST1:

% BRTP $:

ABSTRACT: The conversion of light to mechanical energy is often required in the context of biology and molecular switching. The most straightforward means of accomplishing this is through photoinduced *cis-trans* isomerization in unsaturated systems, e.g. the rhodopsin family of proteins[38].

We have used *ab initio* multi-electronic state quantum dynamics to study the photoinduced isomerization of ethylene[39] and *cis*- and *trans*-butadiene.[*] For ethylene we find that the initial motion is a stretching of the carbon-carbon bond which is followed quite quickly (˜50 femtoseconds after the electronic excitation) by a torsional motion, i.e. *cis-trans* isomerization. Quenching to the ground electronic state is found to be ultrafast and it proceeds from an ionic state via a conical intersection. Accessing the conical intersection requires pyramidalization of one of the methylene groups and this can happen only after energy is funneled from the twisting mode into the pyramidalization mode. These results suggest that conventional one-dimensional torsional potential energy models[40] are inadequate because the multi-dimensional character of the potential energy surface and the accompanying conical intersections are crucial for a realistic picture of the dynamics.

Preliminary results for *cis*- and *trans*-butadiene indicate that for both the *cis* and the *trans* isomers the initial motion on the excited electronic state is a contraction (extension) of the single (double) carbon-carbon bonds. In the case of *cis*-butadiene we also observe a rapid hindered torsional motion of the carbon molecular backbone. During the first 250 femtoseconds following the

[*] URL: http://hobbes.scs.uiuc.edu/

electronic excitation, we do not see any isomerization on the excited electronic state nor a decay to the ground electronic state.

In the future we plan to extend these studies to longer polyenes and to condensed phases and protein environments.

BTA UNIT: T, D

TITLE: Interactive Steered Molecular Dynamics and the Haptic Device

KEYWORDS: Computational steering, haptic, molecular dynamics, human-computer interactions

AXIS I: 9

AXIS II: 74h

INVEST1: Justin Gullingsrud

DEGREE1: B.A.

DEPT1: Department of Physics

INVEST2: John E. Stone

DEGREE2: M.S.

DEPT2: The Beckman Institute

NONHOST1:

% BRTP $: 2.5% (T), 3% (D)

ABSTRACT: The Resource is developing a method for performing Interactive Molecular Dynamics (IMD) simulations.* IMD is a natural extension of the Steered Molecular Dynamics (SMD) simulations developed by our group[8]. IMD will enable the user to manipulate running molecular dynamics simulations of biological macromolecules in real time. In addition to the visual feedback that has been achieved in the field of computational steering[41], IMD would provide force feedback by means of a haptic device.

The haptic device would apply forces exerted by the user to the molecular dynamics simulation, and transmit the resulting reaction forces back to the user. There are at least two advantages to this approach over the more traditional batch job style of MD simulations. First, an investigator could potentially identify plausible or interesting reaction paths, domain movements, or ligand docking sites much more quickly than by running remote batch jobs. Second, haptic feedback opens the door to a faster and much more intuitive understanding of the nature of the forces within complex macromolecules. Understanding protein-ligand interactions via computer simulation is an important part of modern drug design, and could be enhanced significantly by this technology.

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

An IMD session would be composed of several components. The haptic device is connected to a PC, which is responsible for generating the haptic environment experienced by the user. A supercomputer, such as the Origin 2000 at the National Center for Supercomputer Applications (NCSA) or the Cray T3E at the San Diego Supercomputer Center (SDSC) simulates the biological system at speeds of 1 ps of simulation time per second of real time, using the scaleable molecular dynamics program NAMD2[11]. In this way, biologically interesting motions could be investigated interactively. Our molecular graphics program VMD[9] would provide the visualization necessary to enable real-time computational steering of the biological system. The group has already developed a set of protocols, MDCOMM[42], that enables VMD to obtain atomic coordinates from the running simulation. In combination with the Virtual Reality Peripheral Network (VRPN), a library developed at the University of North Carolina, force information is exchanged between the haptic device and the simulation.

BTA UNIT: T, D

TITLE: Time Series Analysis of Molecular Dynamics Trajectories

KEYWORDS: WHAM, Langevin, Onsager-Machlup action, molecular dynamics, protein-ligand

AXIS I: 9

AXIS II: 74f,h

INVEST1: Justin Gullingsrud

DEGREE1: B.A.

DEPT1: Department of Physics

NONHOST1:

INVEST2: Rosemary Braun

DEGREE2: B.A.

DEPT2: Department of Physics

NONHOST2:

% BRTP $: 2% (T), 2% (D)

ABSTRACT: Atomic force microscopy (AFM) experiments[43,44] and Steered Molecular Dynamics (SMD) simulations[45-48,12] have revealed much about the dynamics of protein-ligand binding and unbinding, as well as the stretching and unfolding of proteins. Both techniques induce ligand unbinding or protein unfolding by applying external mechanical forces to the ligand or stretched protein. However, comparing results from these two techniques, such as the magnitude of forces required to unbind ligands, has remained a challenge since SMD simulations proceed six to nine orders of magnitude faster than their experimental counterparts due to limitations in computational resources.

Results of simulations and experiments can be compared through a potential of mean force (PMF). We have described and implemented three time series analysis techniques for reconstructing the PMF from displacement and applied force data gathered from SMD trajectories[49].* One technique, based on the WHAM theory[50], views the unbinding or stretching as a quasi-equilibrium process. The other two techniques assume a Langevin description of the dynamics[51] in order to account for the nonequilibrium

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

character of SMD data. One, which we refer to as the Gaussian drift method, is based on a low noise approximation due to van Kampen[52]; the second, the “least squares method”, is based on a least squares minimization of the Onsager-Machlup action with respect to the choice of PMF.

These analysis methods were tested on one-dimensional model systems for which the underlying PMF was exactly known. The WHAM method systematically overestimated the potential at large displacements because it made no allowance for the irreversible work done during the simulations. The Gaussian drift and least squares methods were applied to actual SMD simulation data from a phospholipid membrane monolayer system[48]. Results of PMF reconstruction using the latter two methods exhibited several important features. First, the peaks in the applied force lined up with the steepest parts of both PMF reconstructions. Second, the height of the potential barrier at the first peak is approximately 1.5 kcal/mol, an appropriate height value for the breaking of a single hydrogen bond. Third, the two independent methods give nearly identical results when presented identical data.

BTA UNIT: C

TITLE: Multi Resolution Description of Biological Systems

KEYWORDS: DNA, theory of elasticity, Kirchhoff equations

AXIS I: 2, 9

AXIS II: 74g

INVEST1: Alexander Balaeff

DEGREE1: M.S.

DEPT1: Center for Biophysics and Computational Biology

NONHOST1:

INVEST2: L. Mahadevan

DEGREE2: Ph.D.

DEPT2: Mechanical Engineering

NONHOST2: Massachusetts Institute of Technology

% BRTP $: 2%

ABSTRACT: Protein-DNA aggregates are involved in key processes in living cells[53,54] and the modeling of these aggregates is essential for understanding these processes. Usually, an all-atom model is required to adequately describe the key parts of the aggregates, such as the protein-DNA interfaces. However, other parts of the system, such as long DNA loops, can be adequately represented by the forces they impose on the rest of the system. A low resolution model of the DNA loops is sufficient for this goal and saves large computational resources.

Using the theory of elasticity[55] we built a low resolution model of DNA loops of intermediate length (several hundred base pairs).* We approximated the looped DNA by a flexible elastic rod described by several parameters, including curvature, twist, and center line coordinates[56-58]. The parameters were consolidated in a Kirchhoff system of equations[59]. We have built upon our previous work[60] and extended the equations to include electrostatic and van der Waals interactions of DNA with external charged particles (e.g., protein amino acid side chains). These interactions provide a more realistic description of DNA.

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

We applied the modified equations to the test case of a DNA loop clamped by the lac repressor[61]. The resulting changes of the shape of the DNA loop are not significant in this case. However, the improved DNA model will be essential in other biological systems, in which close protein-DNA or DNA-DNA contacts are present. We plan to apply the model to such systems, in particular nucleosomes.

BTA UNIT: C

TITLE: Structure Refinement and Water Placement in Bacteriorhodopsin

KEYWORDS: membrane protein, bioenergetics, free energy calculations

AXIS I: 6, 25g

AXIS II: 74h

INVEST1: Jerome Baudry

DEGREE1: Ph.D.

DEPT1: The Beckman Institute

NONHOST1:

INVEST2: Ferenc Molnar

DEGREE2: Ph.D.

DEPT2: The Beckman Institute

NONHOST2:

% BRTP $: 3%

ABSTRACT: Bacteriorhodopsin (bR) is a transmembrane protein that functions as a light-driven proton pump in the cell membrane of *Halobacterium salinarium*.[*] This ~ 3600 atoms protein contains a chromophore – retinal – covalently linked to a lysine side chain via a protonated Schiff base. After absorption of a photon by bR, retinal undergoes isomerization that leads to the transfer of a proton from the intracellular to the extracellular side of the membrane. Despite its relatively small size, bR is an important model for ion channel proteins, and is closely related to molecules involved in vision in humans and other vertebrates.

Experimental results indicate that water molecules buried in the active site of the protein play an active role in the function of bR. These water molecules create a hydrogen bond network that allows proton transfer across large distances in the protein. However the position of these water molecules is not known with precision.

New high-resolution structures of bR were published by our collaborators, Pebey-Peyroula[62] and Luecke[63]. These crystal structures suggest possible hydration sites, with differences between the two structures. We

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

investigated the stability of water molecules in the active site of the protein, and calculated the probability of occupation of various possible hydration sites in bR using free-energy perturbation methods. We found that various hydration sites are possible, some of them with a low probability of occupation, others with a high probability of occupation. Our results are in excellent agreement with suggestions made on the basis of crystal structures, and help to explain the differences observed in the different crystal structures by quantifying the effect of protein environment on the stability of water in bR. This model has been used to analyze the geometry of the binding site and its relation with pK_a changes during the photocycle[64].

The role of water molecules in the function of the protein is under investigation. Our results show that there is a major water re-arrangement after the isomerization of the retinal. Water molecules are suggested to fine-tune the protein structure so as to allow variations in the hydrogen-bond pattern. This controls the orientation and dynamics of proton transfer. Large-scale conformational rearrangements of bR are responsible for the opening of gates that allow water molecules to change their positions in the protein. This ensures both structural stability and functional activity of the protein.

BTA UNIT: C

TITLE: Modeling of High-density Lipoprotein 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:

% 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, phospholipids, 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[65]. Nascent rHDL particles consist of a phospholipid 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 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[66]. The total system, comprising two apolipoproteins, 160 POPC lipids, and 6,224

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

water molecules, 46,522 atoms in all, was tested via simulated annealing using NAMD 2[11] for a total of 250 ps.

We are proceeding to improve this model by improving the initial modeling of the inter-helical turns and by extending the simulations to a full nanosecond with full electrostatics, periodic boundary conditions, and constant pressure simulation methods. We will replicate these simulations with experimentally studied mutants involving the deletion of one or more helices (helix 5, helices 5 and 6, or helices 7 and 8) and an appropriate number of lipids. We will also determine whether the deletion of 20–30 lipids from the particle improves inter-helical packing in our model.

By studying such mutants we will attempt to demonstrate that the inherent flexibility in the “picket-fence” model tolerates such modification to a larger degree than “belt” models based on the recent crystal structure of lipid-free apoA-I[67].

BTA UNIT: C

TITLE: Probing the Role of Structural Water in a Duplex Oligodeoxyribonucleotide Containing a Water-mimicking Base Analogue

KEYWORDS: dodecamer, analogue, hydration, fluctuation, molecular dynamics, water

AXIS I: 2, 9

AXIS II: 74g, h

INVEST1: Dorina Kosztin

DEGREE1: Ph.D.

DEPT1: The Beckman Institute

NONHOST1:
INVEST2: Richard Gumport

DEGREE2: Ph.D.

DEPT2: Department of Biochemistry

NONHOST2:

% BRTP $: 2%

ABSTRACT: The role of water-mediated hydrogen bonds in protein–DNA interactions and the potential contribution to the thermodynamics of DNA–ligand binding indicates the need to know the precise location of water molecules bound in the DNA minor and major grooves[68-71]. DNA hydration has been studied extensively, both theoretically and experimentally, and conformation-dependent differences in both geometry and extent of hydration for the DNA major and minor grooves were shown[72-76].

Nucleoside analogues offer an alternative means to explore the role of water molecules in DNA and in protein–DNA interactions.* Rockhill, *et al.*[77] suggested that the analogue 2'-deoxy-7-hydroxymethyl-7-deazaadenosine (hm^7c^7dA), might mimic a bound water molecule complexed to an adenine residue in the major groove of DNA. The nucleotide analogue (hm^7c^7dA) replaces the hydrogen bond between one hydrogen of a water molecule and N7 of the purine ring with a covalent bond between the carbon of a methylene group and the C7 of the deazapurine ring. The remaining O-H group of the water molecule is replaced by the hydroxyl group of the analogue. In using the analogue to study the role of water molecules in DNA and/or in protein–DNA interactions, one postulates that the oxygen of the

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

hydroxymethyl group is functionally equivalent, as a hydrogen bond acceptor, to the oxygen of the water molecule and that it will be similarly located. Other assumptions are that the analogue will neither disrupt base pair stacking nor hydration properties of normal B-form DNA. This molecular dynamics study was initiated to investigate these assumptions.

One nanosecond molecular dynamics simulations were performed on models of the double-stranded dodecamer DNA, $d(CGCGAATTCGCG)]_2$[78], in which each of the adenine residues, individually or jointly, was replaced by the water-mimicking analogue hm^7c^7dA[77]. For each of the 4 simulated systems, a water bath and counterions were added, resulting in models with approximately 12,000 atoms.

The results show that the simulated systems have structures that remain remarkably similar to the crystal structure[78]. Helix bending toward the major groove at G-A and T-C steps, and some degree of unwinding were observed in all systems, with the most prominent effect in the simulation of DNA with double substitutions. Substitution of both adenine bases with the analogue led to higher fluctuations of the DNA (reflected in the RMSD and the DNA axis fluctuations) than when a single base was replaced. The simulations revealed that the postulated intramolecular bond between the exocyclic amino group of the analogue and the hydroxymethyl group was maintained during the entire simulation. Rotations of the hydroxyl group, observed over short times, provide the flexibility necessary to adapt to conformations required for proteins that bind specifically to it[77]. Analysis of hydration of the major groove showed that the hydroxymethyl group of the analogue replaces the hydration site found above an adenine base, without affecting the hydration of the neighboring bases, when a single base is replaced by the analogue. The simulations, when compared to those of the dodecamer itself, showed that incorporation of the analogue affects neither the overall DNA structure nor its hydrogen-bonding and stacking interactions when a single individual base is replaced by the analogue. The results suggest that the analogue provides a good mimic of specific “ordered” water molecules observed in contact with the DNA itself and in protein-DNA complexes[79].

BTA UNIT: C

TITLE: Structure and Dynamics of Calmodulin in Solution

KEYWORDS: calmodulin, muscle protein, elasticity, steered molecular dynamics, atomic force microscopy

AXIS I: 9, 20

AXIS II: 42, 74c, 77

INVEST1: Hui Lu

DEGREE1: M.S.

DEPT1: Department of Nuclear Engineering

NONHOST1:

INVEST2: Julio Fernandez (and colleagues)

DEGREE2: Ph.D.

DEPT2: Department of Physiology and Biophysics

NONHOST2: Mayo Clinic

% BRTP $: 1%

ABSTRACT: The calcium-sensing protein calmodulin (CaM) exemplifies the function of protein domain movement in the regulation of cellular processes. CaM adopts a dumbbell conformation in which the long helix connecting the two calcium binding domains is completely extended[80].

Steered molecular dynamics (SMD) simulations and atomic force microscopy (AFM) experiments have been applied to study the mechanical stability of CaM under external stretching forces.* Stretching single CaM by SMD showed that there is no dominant force peak in the force-extension profile. Corresponding AFM experiments of stretching poly-CaM provided consistent force recordings. Thus, both SMD simulations and AFM experiments have demonstrated that CaM has little resistance to stretching forces[12,13]. This is clearly different from the previous AFM and SMD studied immunoglobulin (Ig) and fibronectin type III (FnIII) domains that are strongly resistant to mechanical strain. The difference between CaM and Ig/FnIII can be attributed to the different backbone hydrogen bonding patterns of these domains.

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

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: Department of Nuclear Engineering

NONHOST1:

INVEST1: Barry Israelewitz

DEGREE1: M.A.

DEPT2: Center for Biophysics and Computational Biology

NONHOST2:

INVEST3: Julio Fernandez

DEGREE3: Ph.D.

DEPT3: Department of Physiology and Biophysics

NONHOST3: Mayo Clinic

% BRTP $: 3%

ABSTRACT: Atomic force microscopy and Steered Molecular Dynamics (SMD) investigations of the response of so-called mechanical proteins like titin, tenascin or their individual immunoglobulin and fibronectin type III domains have lead to qualitative insights about the relationship between the β sandwich domain architecture and the function of this class of proteins[6,7,81]. The proteins, linear segments of up to hundreds of domains, through strain induced shape changes, unfolding and refolding, maintain order and elasticity in cellular systems over a nearly tenfold length scale.

Steered molecular dynamics simulations[8] were used to study the response of titin's immunoglobulin domain I27 at the onset of domain unfolding.* The

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

results were in quantitative agreement with AFM observations[12,13]. We showed that if forces stronger than 50 pN are applied to the terminal ends the two hydrogen bonds between the antiparallel A and B β-strands break with a concomitant 6-7Å elongation of the protein. If forces strong enough to unfold the domain are applied, the protein is halted in this initial extension until the set of all six hydrogen bonds connecting strands A' and G break simultaneously. This behavior is accounted for by a barrier separating folded and unfolded states, the shape of which is consistent with AFM and chemical denaturation data. We also demonstrate that SMD simulations that induce unfolding through slow pulling (speed 0.1 Å/ps) predict unfolding forces that are within a factor of two of force values extrapolated from AFM observations.

BTA UNIT: C

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

KEYWORDS: ubiquinol, quinone, cytochrome, oxidoreductase, Rieske, ISP, steered molecular dynamics, torque

AXIS I: 2, 9

AXIS II: 74h

INVEST1: Sergei Izrailev

DEGREE1: M.S.

DEPT1: Department of Physics

NONHOST1:

INVEST2: Barry Isralewitz

DEGREE2: M.A.

DEPT2: Center for Biophysics and Computational Biology

NONHOST2:

INVEST3: Antony Crofts

DEGREE3: Ph.D.

DEPT3: Center for Biophysics and Computational Biology

NONHOST3:

INVEST4: E.A. Berry

DEGREE4: Ph.D.

DEPT4:

NONHOST4: Lawrence Berkeley National Laboratory

% BRTP $: 2%

ABSTRACT: Crystallographic structures of the mitochondrial ubiquinol: cytochrome *c* oxidoreductase (cytochrome bc_1 complex) exhibit a substantial movement of

the soluble head of the Rieske iron-sulfur protein (ISP) between reaction domains in cytochrome *b* and cytochrome c_1 subunits[82-84].

We investigated the mechanism governing the rotation of the ISP head by means of Steered Molecular Dynamics (SMD) simulations.[8] External forces were applied to the ISP and the resulting torque induced a rotation of the soluble domain of ISP by 56º within 1 nanosecond. A solvated structure of the bc_1 complex in a phospholipid bilayer (a total of 206,720 atoms) was constructed and a subset of 91,061 atoms was simulated with 45,131 moving atoms. Point charge distributions for the force field parameterization of heme groups and the Fe_2S_2 cluster of the Rieske protein included in the simulated complex were determined. The simulations showed that rotation of the soluble domain of ISP is actually feasible. Several metastable conformations of the ISP during its rotation were identified and the interactions stabilizing the initial, final and intermediate positions of the soluble head of the ISP domain were characterized.

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, enzymatic selectivity

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 $: 3%

ABSTRACT: Molecular Dynamics simulations with external forces [85,45,86,46,47,87,48,8,11,88] were employed to study the unbinding and binding of fatty acids in the cyclooxygenase (COX) site of Prostaglandin H_2 Synthase-1 (PGHS-1). PGHS-1 catalyzes the transformation of the essential fatty acid, arachidonic acid (AA), to prostaglandin H_2 (PGH2).* The COX reaction is the first committed step in the arachidonate cascade leading to the synthesis of various physiologically important prostaglandins[89-92]. Non-steroidal anti-inflammatory drugs (aspirin, flurbiprofen) inhibit the transformation (cyclooxygenation) of AA to prostaglandin G2 (PGG2) which is the precursor to PGH2.

Based on the crystal structure of PGHS-1 (10,000 atoms), with flurbiprofen bound at the active site[93], a model for AA embedded in the enzyme was built in order to study binding mechanism and selectivity of the enzyme[94]. Simulations with the natural COX substrate, AA, inside the COX binding channel reveal sequences of concerted bond rotations in the fatty acid alkyl chain which obviate the need for gross conformational changes in the protein and substrate during unbinding and binding. Two derivatives of AA, one with

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

a *cis* double bond changed to a *trans* configuration and the other with a double bond reduced to a single bond, are also studied. In both cases the concertedness of bond rotations in the fatty acid chain is diminished and larger forces are required to move the fatty acid inside the COX channel. Thus, the all-*cis* structure of AA, with double bonds separated by two single bonds, facilitates easy access to the COX channel and correct positioning inside the active site for the COX chemistry to occur. While no large scale conformational changes in the protein are observed, important motions of residues near the mouth of the COX channel are found and analyzed. In particular, a conformational "switch" involving Arg83, Glu524 and Arg120 is seen to mediate the movement of the substrate from the membrane to the channel.

First results obtained for the exit of the COX reaction product (PGG2) from the binding channel already indicate that the protein must undergo larger conformational changes in order to accommodate movement of the more bulky PGG2. This type of investigations will be extended to inhibitors of PGHS.

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: Ph.D.

DEPT1: The Beckman Institute

NONHOST1:

INVEST2: John Katzenellenbogen

DEGREE2: Ph.D.

DEPT2: Department of Chemistry

NONHOST2:

% BRTP $: 2%

ABSTRACT: The action of retinoic acid (RA), an important regulator of cellular proliferation and differentiation in higher eukaryotes, is mediated by the retinoic acid receptor (RAR). Hormone binding to RAR initiates a series of molecular events culminating in the activation or repression of transcription of target genes. The transition between the bound and unbound form of the retinoic acid receptor is accompanied by a conformational change that enables the hormone-receptor complex to bind to specific sequences of DNA and other transcriptional coactivators or repressors[95-97].

Using Steered Molecular Dynamics[8], we studied the hormone binding/unbinding process in order to clarify the role of some of the amino acid contacts and identify possible binding (unbinding) pathways of the all-*trans* retinoic acid (t-RA) binding (unbinding) to (from) the human retinoic acid receptor (hRAR)-γ.* The crystal structure of the ligand binding domain of RAR bound to t-RA[98] was used. The simulated systems contained the protein, the t-RA hormone and a water bath, resulting in a system of 14,574 atoms. All simulations were performed using the molecular dynamics

* URL: http://www.ks.uiuc.edu/Research/pro_DNA/ster_horm-rec/

program NAMD[10]. Unbinding of the hormone was induced along three pathways selected by a visual examination of the RAR crystal structure[98] done with VMD[9].

Simulation results indicated that it is possible to unbind the hormone along two of the selected pathways without greatly affecting the structure of the protein[88]. Particular characteristics of the simulated pathways suggest a *binding pathway* for the hormone and an alternative "back door" *unbinding pathway*. Using the reversed order of events observed in the simulation we can describe the binding (unbinding) mechanism of the hormone as follows. First, along the *binding pathway*, residue Arg413, and then Arg396 attract and orient the carboxylate end of the hormone towards the binding pocket. When within hydrogen bonding distance of these two residues, the hormone experiences the influence of charged and polar residues located at the opposite end of the binding pocket. The strong electrostatic attraction between the carboxylate end of the hormone and these residues helps the hormone to pass between protein residues, thus, leading to the penetration of the hormone into the binding pocket. The highly fluctuating residues surrounding the entrance may become more ordered upon binding of the hormone, making contacts with the hormone and other protein residues. Unbinding of the hormone may proceed along the *binding pathway* or along an alternative path, the *unbinding pathway*. The dissociation of the hormone along the *unbinding pathway* would be a slow process governed by thermal fluctuations. Presence of ions around that region in the protein as well as intrusion of water molecules in the binding pocket may help destabilize the hydrogen bonding network between the carboxylate end of the hormone and protein residues and, thus, lead to the opening of the binding pocket.

BTA UNIT: C

TITLE: Maturation of Antibody/Antigen Interactions

KEYWORDS: catalytic, antibody, antibody maturation, abzyme 48G7

AXIS I: 2, 9

AXIS II: 64; 74c,h

INVEST1: Jerome Baudry

DEGREE1: Ph.D.

DEPT1: The Beckman Institute

NONHOST1:

INVEST2: Michael Chaney

DEGREE2: Ph.D.

DEPT2: The Beckman Institute

NONHOST2:

INVEST3: Christian Forst

DEGREE3: Ph.D.

DEPT3: The Beckman Institute

NONHOST3:

INVEST4: Ferenc Molnar

DEGREE4: Ph.D.

DEPT4: The Beckman Institute

NONHOST4:

INVEST5: Hui Lu

DEGREE5: M.S.

DEPT5: Department of Nuclear Engineering

NONHOST5:

% BRTP $: 3%

ABSTRACT: Our work focussed on building models for studying conformational differences of four different crystal structures of the catalytic antibody and its mature form 48G7[20] (wild type bound to antigen, wild type unbound, mature bound to antigen, mature unbound).*

We performed semi-empirical calculations to obtain a set of parameters for the antigen molecule, a nitrophenyl phosphonate transition state analog. The four crystal structures were hydrated with a thin (10Å) hydration shell, leading to a total system size of ˜60,000 atoms. Molecular dynamics simulations of these systems were performed using the CHARMM program[23] at room temperature for up to 450 ps for each antibody structure. We observed that during the early stages of the molecular dynamics runs the flexibility of the wild type antibody is higher than that calculated for the mutant antibody, as was suggested by the crystal structures. However, the thin hydration shell we used led to a severe distortion of the antibody structure, and therefore introduced artifacts for long simulation times. A simulation test performed with a larger spherical hydration shell allows a good preservation of the antibody structure, but at the price of a higher computational overhead (total size of more than 100,000 atoms).

New molecular dynamics simulations will be performed on these antibodies with a large hydration shell. Because of the large size of these systems, we will use the highly parallelized molecular dynamics program NAMD2[11] to achieve calculations in a reasonable time. These equilibrated structures will be used in Steered Molecular Dynamics[8] studies of the non-equilibrium process of structural rearrangement upon antigen unbinding.

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

BTA UNIT: C

TITLE: Gold Binding Protein

KEYWORDS: biosensors, gold, molecular dynamics

AXIS I: 2

AXIS II: 74h

INVEST1: Rosemary Braun

DEGREE1: B.S.

DEPT1: Department of Physics

NONHOST1:

INVEST2: Michael Chaney

DEGREE2: Ph.D.

DEPT2: The Beckman Institute

NONHOST2:

INVEST3: Ferenc Molnar

DEGREE3: Ph.D.

DEPT3: The Beckman Institute

NONHOST3:

INVEST3: Mehmet Sarikaya

DEGREE3: Ph.D.

DEPT3: Materials Science and Engineering

NONHOST3: University of Washington, Seattle

% BRTP $: 2%

ABSTRACT: The hard tissues of biological organisms are primarily composed of inorganic materials. The biological control of crystal morphology is requisite for the formation of hard tissue. Sarikaya, et al. have developed a genetic system to isolate proteins that control gold crystallization. It was found[99] that the

gold-binding proteins (GBP) preferentially bound to the (111) face of gold compared with control proteins that do not induce (or retard) gold crystallization.

It is thought that the obscuring of the (111) surface of gold by the bound protein plays a role in the mechanism by which GBP alters crystal morphology. It is still not understood how GBP, which does not contain cysteine (known to form a covalent linkage with gold), adheres to the gold surface. We seek to model and study via steered molecular dynamics[8] the binding of GBP to the (111) crystal surface of gold.*

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

BTA UNIT: C

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 $: 6%

ABSTRACT: The information provided by completely sequenced genomes can yield insights into the multi-level organization of organisms and their evolution. At the lowest level of molecular organization individual enzymes are formed, often through assembly of multiple polypeptides, and at a higher level, sets of enzymes group into metabolic networks[1,4,100]. Much has been learned about the relationship of species from phylogenetic trees comparing individual enzymes.

We have extended conventional phylogenetic analysis of individual enzymes in different organisms to the organisms' metabolic networks.* For this purpose, we suggested a method that combines sequence information with information of the underlying networks[2,3]. We defined a global distance between pathways that incorporates distances between substrates and distances between corresponding enzymes. The new analysis was applied to electron-transfer and information processing networks yielding a more comprehensive understanding of similarities and differences between organisms.

* URL: http://www.ks.uiuc.edu/Method/bioinformatics/

BTA UNIT: C

TITLE: Magnetic Sensor

KEYWORDS: magnetoreception, radical pair processes, photoreceptors

AXIS I: 1d, 25

AXIS II: 74h

INVEST1: Thorsten Ritz

DEGREE1: B.S.

DEPT1: Department of Physics

NONHOST1:

INVEST2: John B. Phillips

DEGREE2: Ph.D.

DEPT2: Department of Biology

NONHOST2: Indiana University, Bloomington

% BRTP $: 2%

ABSTRACT: A large variety of animals have been shown to utilize the earth's magnetic field for orientation. However, the mechanism of magnetoreception in vertebrates is one of the few sensory mechanisms for which no receptor has yet been identified. Behavioral experiments show that the magnetoreception mechanism in birds[101] and newts[102] requires the presence of light with an energy higher than a threshold energy in order to work properly. These experiments suggest a magnetoreception mechanism involving photoreceptors. Radical-pair processes induced by light-absorption in a photoreceptor have been shown to be sensitive to magnetic fields[103], but it is not clear whether a field as weak as the earth's magnetic field (0.5 Gauss) can produce significant effects.

We calculate, on the basis of quantum mechanics, the effect of weak magnetic fields on an orientationally ordered system of molecular substrates performing radical pair processes as a model for a magnetoreception organ.[*] These calculations specify conditions where a magnetic field of 0.5 Gauss can produce significant effects[104]. With additional assumptions about the sensory transduction pathway, predictions about the behavioral responses can be made and are found to be in good agreement with experiments. These

[*] URL: http://www.ks.uiuc.edu/Research/magsense/ms.html/

calculations represent a step towards singling out a promising candidate for a magnetoreception mechanism in animals and towards designing experiments to test this suggestion.

BTA UNIT: C

TITLE: Excitation Energy Transfer in Carotenoid-Chlorophyll Assemblies

KEYWORDS: light-harvesting complexes, energy transfer, carotenoids, bacteriochlorophylls, quantum mechanics

AXIS I: 7a, 9

AXIS II: 74h

INVEST1: Ana Damjanovic

DEGREE1: B.S.

DEPT1: Department of Physics

NONHOST1:

INVEST2: Thorsten Ritz

DEGREE2: B.S.

DEPT2: Department of Physics

INVEST3: Xiche Hu

DEGREE3: Ph.D.

DEPT3: Department of Chemistry

NONHOST3: University of Toledo, Ohio

INVEST4: Lubos Mitas

DEGREE4: Ph.D.

DEPT4: NCSA

NONHOST4:

% BRTP $: 3%

ABSTRACT: Photosynthetic organisms, i.e. plants, algae, and photosynthetic bacteria, developed very efficient chromophore-protein complexes [known as the photosynthetic unit (PSU)] to harvest the light of the sun and to utilize its energy to drive photoinduced chemical reactions. The PSU of purple bacteria is a nanometric assembly of light-harvesting complexes (LH) which surround

the so-called photosynthetic reaction center (RC), and contains hundreds of individual alpha-helical segments and thousands of chromophores [bacteriochlorophylls (BChls) and carotenoids]. Determination of the crystal structure of the light-harvesting complex LH-II[105,106] as well as modeling of the atomic structure of the light-harvesting complex LH-I[107] which directly surrounds the photosynthetic reaction center[108,109], yield a complete picture of chromophore organization in the PSU. The resulting model structure of the PSU provides a framework for studying the funneling of electronic excitation energy to the RC.*

Through Förster theory and effective Hamiltonian description[110] of the electronic states of LH-I we have studied the rate-determining step in excitation energy transfer in the PSU, namely LH-I $\rightarrow$ RC transfer[111]. We discussed the role of accessory RC BChls, as well as of delocalization length of LH-I excitons in the excitation energy transfer.

The theoretical framework for studying excitation energy transfer between carotenoids and BChls was established in [112,113]. Based on the availability of chromophore geometries and on configuration interaction (CI) expansions of the electronic states of individual chromophores, the excitation energy transfer between carotenoids and BChls was described by means of Fermi's golden rule. The electronic coupling between various electronic excitations is determined for all orders of multipoles (Coulomb mechanism) and it includes the electron exchange (Dexter mechanism) term. The method has been successfully applied to two light-harvesting complexes, LH-II of purple bacteria[113] and peridin-chlorophyll-protein (PCP) of dinoflagellates. For both proteins the calculations identified the Coulomb mechanism as the dominant mechanism of singlet excitation energy transfer. The pathways of excitation energy transfer were also identified.

We plan to continue the research on light-harvesting complexes and characterize the nature of electronic excitations of LH-II *in situ* by establishing a computational model of LH-II (70,000 atoms) integrated into a lipid bilayer with appropriate water layers.

* URL: http://www.ks.uiuc.edu/Research/psu/psu.html/

BTA UNIT: C

TITLE: The RGD Loop of Fibronectin Type III Module is Revealed as a Tensile Molecular Recognition Switch

KEYWORDS: fibronectin, RGD loop, SMD, tensile, force, adhesion, integrin

AXIS I: 13, 20

AXIS II: 74h

INVEST1: Hui Lu

DEGREE1: M.S.

DEPT1: Department of Nuclear Engineering

NONHOST1:

INVEST2: Barry Israelewitz

DEGREE2: M.A.

DEPT2: Center for Biophysics and Computational Biology

INVEST3: Viola Vogel

DEGREE3: Ph.D.

DEPT3: Bioengineering

NONHOST3: University of Washington, Seattle

% BRTP $: 4%

ABSTRACT: The tenth type III module of fibronectin, $FnIII_{10}$, possesses a β-sandwich structure consisting of seven β-strands (A–G) that are arranged in two anti-parallel sheets[114,14]. It mediates cell adhesion to surfaces via its integrin binding motif[15,75], Arg78, Gly79, and Asp80 (RGD), that is placed at the apex of the loop connecting the two successive β-strands, strands F and G.*

Steered Molecular Dynamics (SMD) simulations[47,48] in which tension was applied to the protein's terminal ends revealed that β-strand G is the first to break away from the module upon forced unfolding, while the remaining fold maintains its structural integrity[16]. The separation of strand G from the remaining fold resulted in a gradual shortening of the distance between the

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

apex of the RGD-containing loop and the module surface which potentially reduces the loop's accessibility to surface-bound integrins[17]. The shortening is followed by a straightening of the RGD-loop from a tight β-turn into a linear conformation which suggests a further decrease of affinity and selectivity to integrins. The RGD-loop is therefore strategically located to undergo strong conformational changes in the early stretching stages of the module, and thus constitutes a mechanosensitive control of integrin recognition.

The structure of the integrin which binds the RGD loop will become available shortly. Future work will use this structure to model the tensile response of a docked $FnIII_{10}$-integrin system, to study details of the mechanism of the recognition switch.

BioCoRE - Collaboratory for Structural Biology[1]

In February 1999 the Resource began developing BioCoRE (Biological Collaborative Research Environment) to support collaboration in the field of structural biology. The project is funded through an NIH supplemental award to establish a collaboratory testbed. BioCoRE is designed to facilitate collaborative work between biomedical researchers located at the same or geographically distant sites. A web-based interface will enable the transparent use of, and communication between, programs, tools, and databases. The collaboratory software will allow researchers to interact in both synchronous and asynchronous ways with each other or with modeling tools. The collaboratory software will facilitate the sharing of informational, computational as well as data-storage resources.

BioCoRE will support four basic types of activities: (1) utilizing a wide range of computational tools; (2) keeping records; (3) communicating with collaborators; (4) writing multi-author articles and reports. This functionality will be implemented in four main components of BioCoRE, called *Workbench*, *Notebook*, *Conferences*, and *Documents*. A built-in evaluation component will guarantee an ongoing assessment of the BioCoRE development and effectiveness of the new environment.

The initial stages of the Collaboratory project were devoted to personnel hiring, basic software design decisions, securing of space, and equipment acquisitions. Currently two of the three programmer positions for the project are filled. The first programmer started working on BioCoRE on April 15 and will be joined by the second programmer on June 1. The third position is still vacant and the search for an appropriate candidate is in full force. The recruitment of research assistants for the project is progressing. A social science student who will do the evaluation work will start this summer. We hope that the others will join the project in the fall, with the beginning of the new academic year.

A preliminary survey of existing collaboratories (Space Physics and Astronomy Research Collaboratory[2], EMSL Collaborator[3], DOE2000[4], An Electronic MIS Collaboratory on the World Wide Web[5]) indicates that most are based on a client/server approach with a common Java enabled web-browser as the basic user interface. A similar strategy will be adopted for BioCoRE. The usefulness of existing software paradigms (Stanford NRE Collaboratory System[6], EMSL Collaboratory[3], NCSA Habanero[7], TANGO Interactive Web Collaboratory[8]) for the aims of BioCoRE is currently being evaluated.

Utilizing the additional insight gained from the evaluation of existing collaboratories, one of the first steps of the development work in the next year will be the design and implementation of the Collaboratory Interface which enables the interaction of the different components of BioCoRE. Simulation monitoring and control capabilities will be available through the *Workbench*. The molecular graphics program of the Resource (VMD) will be enabled to interact closely with the

[1] URL: http://www.ks.uiuc.edu/Research/collaboratory/
[2] URL: http://www.crew.umich.edu/UARC/background.html/
[3] URL: http://www.emsl.pnl.gov:2080/docs/collab/CollabHome.html/
[4] URL: http://www-unix.mcs.anl.gov/DOE2000/
[5] URL: http://cism.bus.utexas.edu/collab.html/
[6] URL: http://www-flash.stanford.edu/collab/projects.html/
[7] URL: http://havefun.ncsa.uiuc.edu/habanero/
[8] URL: http://trurl.npac.syr.edu/tango/

molecular dynamics simulation program developed at the Resource (NAMD). Annotation and logging of simulation results will be provided through basic *Notebook* communication and record keeping capabilities. Shared whiteboards and visualization will provide means for communication through the *Conferences* tool. The recent upgrade of the networking facilities at the Beckman Institute to 100BaseT is an excellent opportunity to optimize the performance of the Collaboratory components on our Intranet. The availability of *vBNS*[9] through our partnership with NCSA[10] will allow us to expand a Collaboratory environment, even with high throughput demands, to distant sites.

[9] URL: http://www.vbns.net/
[10] URL: http://access.ncsa.uiuc.edu/Briefs/990223.FasterVBNS.html/

	TECH RES & DEVEL (T)	COLLAB RES & SERVICE (C)	DISSEM & TRAINING (D)	TOTALS
NUMBER OF PUBLICATIONS	32	9	4	45
NUMBER OF SUBPROJECTS	8	15	4	27*
NUMBER OF INVESTIGATORS	10	26	6	42*
PERCENT OF BRTP FUNDS ALLOCATED	35%	40%	25%	100%
SERVICE FEES COLLECTED	0	0	0	0
OTHER FUNDS ($)	200,000	135,000	—	335,000

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

State or Country	Number of Investigators
IL	27
WA	2
CA	1
MA	1
MN	1
IN	1
OH	1

BRTP Unit T

Investigator	Non-Host Institution (Principle Investigator)	Sources of Support	
		TYPE	AGENCY
Ben-Nun, Michal	University of Illinois (Martinez, Todd)	FED	NIH
Braun, Rosemary	University of Illinois (Schulten, Klaus)	OTH/FED	NIH
Brown, Charles R.	University of Illinois (Schulten, Klaus)	FED	NIH
Brunner, Robert	University of Illinois (Kale, Laximkant)	FED	NIH
Hardy, David	University of Illinois (Skeel, Robert)	FED	NIH
Izaguirre, Jesus	University of Illinois (Skeel, Robert)	FED	NSF
Gullingsrud, Justin	University of Illinois (Schulten, Klaus)	OTH	
Phillips, Jim	University of Illinois (Schulten, Klaus)	FED	DOE
Stone, John E.	University of Illinois (Schulten, Klaus)	FED	NIH
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
Crofts, Anthony	University of Illinois (Crofts, Anthony)	FED	NIH
Chaney, Michael	University of Illinois (Schulten, Klaus)	FED	NIH/NSF
Damjanovic, Ana	University of Illinois (Schulten, Klaus)	OTH	
Fernandez, Julio	Mayo Clinic (Fernandez, Julio)	FED	NIH
Forst, Christian	University of Illinois (Schulten, Klaus)	FED	NIH
Gumport, Richard	University of Illinois (Gumport, Richard)	FED	NIH
Hu, Xiche	University of Toledo, OH (Hu, Xiche)	OTH	
Isralewitz, Barry	University of Illinois (Schulten, Klaus)	OTH/FED	NIH
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
Mahadevan, L.	MIT, MA (Mahadevan, L.)	FED	NIH
Mitas, Lubos	NCSA, IL (Mitas, Lubos)	FED	NIH/NSF

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
Phillips, John B.	University of Indiana, Bloomington (Phillips, John B.)	FED	NIH/NSF
Ritz, Thorsten	University of Illinois (Schulten, Klaus)	FED/OTH	NIH
Sarikaya, Mehmet	University of Washington, Seattle (Sarikaya, Mehmet)	FED	NIH/NSF
Vogel, Viola	University of Washington, Seattle (Vogel, Viola)	FED	NIH

BRTP Unit D

Investigator	Non-Host Institution (Principle Investigator)	Sources of Support	
		TYPE	AGENCY
Braun, Rosemary	University of Illinois (Schulten, Klaus)	OTH/FED	NIH
Brunner, Robert	University of Illinois (Kale, Laximkant)	FED	NIH
Gullingsrud, Justin	University of Illinois (Schulten, Klaus)	OTH	
Phillips, Jim	University of Illinois (Schulten, Klaus)	FED	DOE
Stone, John E.	University of Illinois (Schulten, Klaus)	FED	NIH
Varadarajan, Krishnan	University of Illinois (Kale, Laximkant)	FED	NIH

BTA unit: (T)
Number Published –
Books: 1 Papers: 25 Abstracts: 0

Number In Press or Submitted –
Books: 0 Papers: 7 Abstracts: 0

Books
Published:

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In Press or Submitted:

None

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Published:

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Abstracts
Published:

None

In Press or Submitted:

None

BTA unit: (C)
Number Published –
Books: 0 Papers: 4 Abstracts: 0

Number In Press or Submitted –
Books: 0 Papers: 5 Abstracts: 0

Books
Published:

None
In Press or Submitted:

None

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Abstracts
Published:

None

IN PRESS OR SUBMITTED:

None

BTA unit: (D)
Number Published –
Books: 0 Papers: 3 Abstracts: 0

Number In Press or Submitted –
Books: 0 Papers: 1 Abstracts: 0

Books
Published:

None

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None

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Abstracts
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None

In Press or Submitted:

None

Advisory Committee

Report of the Resource Advisory Board of the NIH Resource for Macromolecular Modeling and Bioinformatics September 16, 1998.

All Members of the Board were present: Peter Arzberger (Chair), Bernie Alder (UC Berkeley), Joel Berendzen (LANL), Attila Szabo (NIH), Colin Wraight (UIUC).

Note: The Board also benefited from consultations with John Wooley (DOE), who was present during the visit.

BACKGROUND: The last meeting of this Board was in November 1996. At that time the Resource was preparing the renewal proposal for their Resource. We were happy to learn that this Resource was successfully renewed. Given that this Resource was recently renewed, the goal of this meeting was to evaluate some new directions the Resource was considering to ensure a vital resource at the end of the next 5 years of funding. The Director of the Resource felt that this was an ideal time to consider these questions, and the Advisory Board agreed.

MEETING: Since the focus of this year's review was on the core research, most of the discussion focused on that. It is understood that next year we will hear more about collaborative research.

Dr. Schulten started the presentation by reviewing the highlights of the last year and stating the main joint research goals in 1999:

- Steered Molecular Dynamics
- Simulations of cellular molecular machines (>100,000 atoms) (e.g. photosynthetic apparatus of purple bacteria, proteins as regulators of genomes)
- Microsecond Simulations
- Quantum Simulations of Bacteriorhodopsin.

During the course of our meeting, we observed that the Resource had evolved into new areas: Quantum Mechanical Effects in Proteins, led by Todd Martinez, and A Challenge of Bioinformatics: Evolution of Metabolism, by Christian Forst. In addition, we heard about Steered Molecular Dynamics, led by Klaus Schulten, that integrated many of the technology activities (visualization, molecular dynamics, structural biology) that are a strength of this Resource. We also heard about the technology development projects of Parallel Molecular Dynamics (NAMD2) led by. L. Kale, Integrators for Faster MD Simulations led by Bob Skeel, and the visualization program VMD.

In addition, we heard about Administration, Service, Training, and Dissemination from Dr. Gila Budescu.

ASSESSMENT: Our assessment will treat the new direction of bioinformatics (highlighted by the new title of the Resource) and each of the main goals for 1999 in turn. We also addressed the issue of software, administration, and balance of graduate students versus postdocs.

Overall, we were very impressed with the range of activities, the accomplishments of the last year, and the thought going into the future directions of the Resource. This is a strong Resource. We also are very supportive of steps taken by the Resource in new directions. These types of steps will ensure the vitality and longevity of the Resource. Below are some specific comments, with suggestions. These are intended to improve the quality of the Resource, which is already very high.

Bioinformatics: Schulten felt that the Resource must move in this direction, based on the overall trend in the community and bioinformatic's increasingly important role with the increased data available. Schulten felt that the best strategy to embark in this direction was to hire a senior person in this field. He has done this with Dr. Forst, and with the recruitment of a senior fellow Dr. M. Chaney (although we did not hear directly about the latter's work). In addition, the Advisory Board is aware of the supplementary request for the collaboratory, which would also develop expertise in this area.

The following recommendation to the Resource must be taken in the light that we only heard about Dr. Forst's work, which is only a portion of the activities in bioinformatics. But we strongly recommend that the bioinformatics work be linked tightly with the strengths of the Resource in theory, structural modeling, and parallel computation. Most bioinformatics groups that we are aware of are not strong in these areas and we feel that the Resource could find itself in an important niche in the post-genome era of biology. The Board feels that having a closely-integrated effort would bring synergy to the Resource and would avoid the criticism that the informatics work is more of an R01 project. In addition, we want to ask Dr. Schulten to consider what portion of the Resource's activity is appropriate for Bioinformatics.

In summary, the Advisory Board endorses the move in this important direction, and the strategy of hiring senior expertise to help develop this area. However, the Advisory Board feels strongly that Schulten must make a very strong effort to integrate the directions in bioinformatics within his Resource to the strengths of the Resource, namely structural bioinformatics. Finally, we feel that there are many opportunities in structural bioinformatics, and Schulten should not feel that this area is already well-covered in the community.

Steered Molecular Dynamics: This is one of the four stated goals in 1999. The discussion here focused on issues of

- Add quantification to the plans we saw, which were more qualitative.
- Contrast the results with experimental data (e.g. Force microscope).
- Portion of Resource devoted to this project (the numbers we got were approximately $1/5^{th}$ of the students).
- Value of haptic devices and speech input tools. We learned that technology existed in both of these arenas, and the Resource would integrate them into the system.

We noted that this was an intriguing project that had some risk associated with it. However, as the review of the Resource indicated, Schulten is not afraid of risky projects or to tackle big problems and the reviewers believe these are important prerequistes for a successful Research Resource. The Advisory Board felt that the proportion of the Resource devoted to the project was appropriate, that this project would benefit by adding quantification to the output. The Board agreed with the PI that Schulten should run with the project for a year, see what emerged, and convince the Board that this was moving in a way that would equal the quality of his other projects. We conveyed our lack of enthusiasm for the need of the haptic and speech-input tools, but we are happy to be convinced otherwise.

Simulations of Cellular Molecular Machines (>100,000): This was another of the four main goals for 1999. A couple of the problems associated with this goal include understanding the photosynthetic apparatus of purple bacteria, and the role of proteins as regulators of genomes. The Advisory Board strongly endorsed this activity.

Microsecond Simulations: The major discussion around this project was the lack of a stated motivating example. The Advisory Board feels that this needs to be done, anticipating much

larger machines. There was a comment that the time frame is in the range of experimental results. Comparison with experimental results is important and would be greatly aided by uncertainty estimates.

Quantum Simulations of Bacteriorhodopsin: This is a very good area. The Advisory Board felt that there needed to be some stated motivation of the biology or biomedical sciences in the thinking of this project as it progresses. In particular, the development of new methods and their application to model systems should be supplemented by an all out effort to do a state-of-the-art calculation on the biomolecule, where well-defined biophysical questions, not accessible by classical simulations, are answered.

Software: One main comment made by the Advisory Board is that the Resource should attempt to make software as user friendly as possible, and think beyond the traditional users to the broader community of users who may not be as sophisticated.

The Advisory Board was pleased by the advances and maturing in VMD, and was pleased that the Resource had hired a strong programmer (Stone). The Board also liked the plans for parallelization improvements of NAMD2, and was very encouraged to hear about the hire of a programmer for this work (Phillips).

To make VMD and NAMD2 more accessible, extensible, and available for integration with other tools, the Advisory Board recommends formally defining application product interfaces (API's) for these tools and adhering to them. We believe that the discipline of defining API's will make for better tools as well. Once the API's are defined, providing bindings to languages such as C++ and Python is encouraged.

Regarding the work on Integrators for Faster MD, the Board suggested that there be benchmarks in the future for step sizes, and relate that to release of NAMD.

Balance of Graduate Students versus Postdocs: Schulten indicated a change in strategy from previous years, in the balance between graduate students and postdocs. He is increasing the percentage of postdocs, in part because of the ability to get results more quickly, and in part in light of the shrinking pool of graduate students. The Board discussed this, and only noted that as the graduate students trained by Schulten decrease, the number of postdocs available to the community also decreases.

Administration: It was clear that Gila Budescu is playing a major role in this Resource, and the Advisory Board acknowledged this support and leadership, and this positive effect on the Resource. Her performance has demonstrated the capacity for independence in pursuing tasks that the Resource deems important, and she should be given the resources and encouragement necessary to continue her professional development. Dr. Budescu might be an ideal person to bring the tools and methods developed by the Resource to a much wider user community than the traditional base of computational and experimental structural biologists.

In our ongoing efforts to ensure a close fit between the research and development areas of the Resource and the expertise of the board members, in recent months two of the previous members retired and new members agreed to join. Attila Szabo and Bernie Alder who served for many years on our board, and skillfully guided us with their expert advice, have now retired (from the board). Our renewed advisory board for the next year is:

- Biophysics and Pharmacology – Harel Weinstein, Mount Sinai School of Medicine;
- Biophysics – Colin Wraight, School of Life Sciences, UIUC;

- Structural Biology – Joel Berendzen, Physics Division, LANL;
- Biocomputing – Bernie Brooks, Computational Research and Technology, NIH;
- Bioinformatics – Jeff Skolnick, Scripps Research Institute;
- Computer Science – Dannis Gannon, Computer Science, IU;
- Biomathematics and Scientific Administration – Peter Arzberger, Advanced Scientific Computing, SDSC.

The next meeting at the University of Illinois is scheduled for September 16, 1999.

Service, Training and Dissemination

The Resource's service, training and dissemination areas experienced a highly productive and dynamic year as is evident from the various activities reported below. As always, we have been exploring, and whenever feasible exploiting, all relevant avenues to expand and fortify these functions. The recent Collaboratory award will further strengthen our resolve to offer quality service to the structural biology community. It will also enhance our capabilities to create and sustain a broad spectrum of services. With the collaboratory initiative and intensive recruiting efforts we substantially increased the size of our technical support staff. By this summer we will have established a cohesive and dedicated team of 5 highly qualified programmers ready to fully attain our software development aspirations. A highly skilled system administrator has recently joined the Resource and will ensure the professional support of the cutting edge technology needed to meet our research and development targets.

Service

The services offered by the Resource are enjoyed by a vast number of biomedical researchers, domestic and international. A large fraction of our user population is directly involved with medical research sponsored by the National Institutes of Health (NIH). An estimated 20% of our software (VMD and NAMD) users are NIH supported. Much of the work citing VMD and NAMD is by researchers funded by NIH. Several of the Resource's experimental collaborators are recipients of NIH grants as are speakers invited to participate in our regular seminar series. Moreover, much of the UIUC audience attending the seminars receive NIH support. Last but not least, the meeting Opportunities in Molecular Biomedicine in the Era of Teraflop Computing, organized by the Resource on March 3-4 of this year, brought together world-class biomedical researchers, most of whom are supported by NIH, and senior federal officials from NIH, NSF, DOE, DOD, and others. Details on each of these service endeavors are presented below.

The services we offer may be classified into two broad categories:

- technological services, designed to provide the scientific community with easy access to and use of 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

VMD 1.2 was released on August 1st, 1998. This version of VMD was a major update which improved both functionality and efficiency:

- Rendering speed improved by a factor of five for OpenGL hardware.
- Support for new Unix platforms with OpenGL: AIX, Linux, Solaris, HP-UX.
- Stereoscopic display support for OpenGL platforms.
- Support for Tk graphics.
- Support for MSMS molecular surfaces.
- Support for GRASP file format.
- Many other small improvements and bug fixes.
- Updated documentation available in postscript and HTML.

VMD 1.3 was released on April 5th, 1999. This most recent version of VMD contains many significant improvements over VMD 1.2:

- Decreased overall memory usage by 15%.
- Redesigned snapshot feature for greater portability.
- Many bugs have been fixed in the OpenGL version.
- Eliminated dependence on several external programs.
- OpenGL version now provides rudimentary Cave support.
- Compiles and runs on IRIX 6.x.
- Built with Mesa 3.0 and Tcl/Tk/TclX 8.0.4.
- Numerous improvements to the renderer export functionality.
- Added support for the Tachyon multiprocessor ray tracer.
- Improved built-in help system, updated contents.
- Many improvements to overall efficiency.
- Ported to Solaris x86.
- Fully updated documentation available in postscript and HTML.
- Users can select an image viewer program for use with snapshot feature.

Portability, efficiency, and correctness have been the primary development goals for VMD in the last year. The resulting increase in the number and variety of VMD users has also provided the VMD developers with plentiful feedback, helping to track down and eliminate software bugs. A recent VMD user survey is included in this report (Appendix I).

The VMD web site (http://www.ks.uiuc.edu/Research/vmd/) has been completely overhauled. The site is now more comprehensive and maintainable, and has been restructured for improved readability. To offer VMD users maximal access to information, the web site contains information on the old, new, and in-development versions of VMD (versions 1.2, 1.3, and 1.4 respectively).

VMD release announcements were made to the Usenet newsgroups bionet.announce, bionet.biology.computational, bionet.molec-model, bionet.software, bionet.software.x-plor, comp.sys.sun.announce, comp.sys.sgi.graphics, comp.os.linux.announce and to the computational chemistry list at chemistry@infomeister.osc.edu.

During the period after the release of VMD 1.2 and before the release of VMD 1.3, we received 2,022 registrations, 1,824 binary downloads, 922 source code downloads, and more than 3,000 reported users. Of the binary downloads, 934 were for Linux, 675 for SGI IRIX, 119 for Sun Solaris, 59 for IBM AIX and 37 for HP HP-UX.

Since VMD 1.3 was released on April 5, 1999, more than 700 users have registered and downloaded the program. Of the 700 registered VMD 1.3 users, close to 25% identified themselves as NIH supported researchers. VMD has been installed on the visualization systems of NCSA. Users on those machines are required to register directly with the Resource.

Future VMD development will focus on enhancing user friendliness on all supported platforms. VMD 1.4, scheduled to be released in early Fall 1999, will be the first release of VMD to support Microsoft Windows.

An agreement about to be signed with the Cambridge Crystallographic Data Centre (CCDC) will establish VMD as the standard visualizer of the Cambridge Structural Database (CSD). CSD is CCDC's primary product, offering the largest small-structure database in the world to the

biomedical community, among them NIH sponsored researchers. Similar agreements with other databases and publications are being considered.

NAMD 1.5, the last version in the NAMD 1.X series, was released on September 4, 1998. New in this version of NAMD (since 1.4) were:

- Added features, including rigid bonds and moving harmonic restraints.
- Updated user guide, also available in HTML form.
- Modified to work with PVM 3.4 beta.
- Enhanced performance by as much as 30%.
- Modified to work with the latest version of DPMTA (2.7).
- Included DPMTA source to make installation easier.
- Simplified build process, fewer options to specify, better documentation.
- Several bug fixes.

NAMD 2.0 was released on March 25, 1999. This was preceded by the releases of beta versions 2.0b2 and 2.0b3 on October 10, 1998 and February 3, 1999. Version 2.0 represents a major rewrite of the NAMD 1.X internal structure for speed, scalability, and maintainability while the user-visible interface has remained largely unchanged. New features since version 2.0b1 include:

- Langevin piston Nose-Hoover constant pressure simulation.
- Free energy of conformational change calculation.
- Compatibility with CHARMM formatted parameter files.
- Elimination of force calculations between fixed atoms.

The stability and speed of NAMD have been the foci of development during its extended beta testing period. Many bugs have been fixed which were exposed by large machines such as the Cray T3E and SGI Origin 2000, by slower networking on our local Linux cluster, and by long production runs. Improvements have also been made to the underlying Converse messaging system which replaces PVM in NAMD 2.0. Syntax changes which enhance the readability of messaging calls in NAMD are being incorporated into the source code which will be released as version 2.0.1 in May 1999.

Enhancements planned for future versions of NAMD include:

- Incorporation of the mollified impulse multiple time-stepping method.
- Use of multiple threads per node on clusters of multiprocessors.
- Parallelization of the reciprocal space part of particle mesh Ewald.
- Support for AMBER force fields and file formats.
- Chemical mutation, multiple copy, and other non-physical methods.
- Special features for interactive modeling via haptic feedback.
- Reduction of peak per-node memory use.
- Full scripting of the simulation protocol.

The NAMD web site (http://www.ks.uiuc.edu/Research/namd/) was redesigned in conjunction with the NAMD 2.0b3 release to merge the version 1.X and 2.0 web sites. Versions 1.5 and 2.0 are both represented and will remain so at least until the release of version 2.1. We also began requiring users to register, providing their name, e-mail address, and simple usage information in order to download NAMD. We have found from this information that most users are at academic institutions, both foreign and domestic, and have between one and four users at their site.

Release announcements were made to the Usenet newsgroups bionet.announce, bionet.biology.computational, bionet.molec-model, bionet.software, and bionet.software.x-plor, to the computational chemistry e-mail list at chemistry@infomeister.osc.edu, and to the Beowulf (commodity cluster) announcement e-mail list at beowulf-announce@beowulf.gsfc.nasa.gov.

In the first month since the release of version 2.0 we recorded 100 registrations, of which about 20% are NIH funded. After the initial surge following the announcement new registrations occur at a rate of about two per day, reflecting interest in NAMD generated by software directories, web search engines, and the popularity of the TBG web site.

The following new publications concerning the features and design of NAMD 2.0 have been produced by the Resource in the past year:

L. V. Kale, M. Bhandarkar, R. Brunner, N. Krawetz, J. Phillips, and A. Shinozaki, "NAMD: A Case Study in Multilingual Parallel Programming," in Languages and Compilers for Parallel Computing, Z. Li, P.-C. Yew, S. Chatterjee, C.-H. Huang, P. Sadayappan, and D. Sehr, eds., Volume 1366 Lecture Notes in Computer Science, Springer-Verlag, Berlin, pp. 367–381 (1998).

J. C. Phillips, R. Brunner, A. Shinozaki, M. Bhandarkar, N. Krawetz, L. Kale, R. D. Skeel, and K. Schulten, "Avoiding algorithmic obfuscation in a message-driven parallel MD code," in Computational Molecular Dynamics: Challenges, Methods, Ideas, P. Deuflhard, J. Hermans, B. Leimkuhler, A. E. Mark, S. Reich, and R. D. Skeel, eds., Volume 4 of Lecture Notes in Computational Science and Engineering, Springer-Verlag, Berlin, pp. 472–482 (1999).

R. Brunner, L. Kale, and J. C. Phillips, "Flexibility and Inter-operability in a Parallel Biomolecular Dynamics Code," in Proceedings of the SIAM Interdisciplinary Workshop Object Oriented Methods for Inter-operable Scientific and Engineering Computing, held October 21-23, 1998 at the IBM Research T.J. Watson Research Center, Yorktown Heights, New York, pp. 80–89 (1998).

L. Kale, R. D. Skeel, M. Bhandarkar, R. Brunner, A. Gursoy, N. Krawetz, J. C. Phillips, A. Shinozaki, K. Varadarajan, and K. Schulten, "NAMD2: Greater scalability for parallel molecular dynamics," *J. Comp. Phys*., **151**, 283–312 (1999).

* Over the last 12 months there have been 900 queries from 350 VMD users and 70 queries from 35 NAMD users. We provide user support through e-mail and the average response time, desired and actual, is 48 hours.

VMD CITATIONS

The following publications citing the original VMD paper, as specified in the VMD license agreement, have appeared since May 1998, indicating the use of VMD for their research:

Mayer, B., "Endocytosis: EH domains lend a hand" *Current Biology* **9**, R70-R73 (1999).

Wriggers, W., Schulten, K., "Investigating a back door mechanism of actinphosphate release by steered molecular dynamics," *Proteins* **35**, 262-273 (1999).

Damjanovic, A., Ritz, T., Schulten, K., "Energy transfer between carotenoids and bacteriochlorophylls in light-harvesting complex II of purple bacteria," *Phys. Rev. E* **59**, 3293-3311 (1999).

Sheldahl, C., Harvey, S.C., "Molecular dynamics on a model for nascent high-density lipoprotein: Role of salt bridges," *Biophys. J.* **76**, 1190-1198 (1999).

Baudry, J., Crouzy, S., Roux, B., and Smith, J.C., "Simulation Analysis of the Retinal Conformational Equlibrium in Dark-Adapted Bacteriorhodopsin," *Biophys. J.* **76**, 1909-1917 (1999).

Brautigam, C.A., Sun, S., Piccirilli, J.A., Steitz, T.A., "Structures of normal single-stranded DNA and deoxyribo-3-S- phosphorothiolates bound to the 3-5 exonucleolytic active site of DNA polymerase I from Escherichia coli," *Biochemistry* **38**, 696-704 (1999).

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NAMD CITATIONS

The following publications citing the original NAMD paper, as specified in the license agreement, have appeared since May 1998, indicating the use of NAMD for their research:

Sheldahl, C., Harvey, S.C., "Molecular dynamics on a model for nascent high-density lipoprotein: Role of salt bridges," *Biophys. J.* **76**, 1190-1198 (1999).

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Humphrey, W., Lu, H., Logunov, I., Werner, H. J., Schulten, K., "Three electronic state model of the primary phototransformation of bacteriorhodopsin," *Biophys. J.* **75**, 1689-1699 (1998).

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* Patent/s filed in the past year: "Tensile Molecular Recognition Switch" (with V. Vogel, A. Krammer, H. Lu, B. Isralewitz and K. Schulten).

* The Resource's computational facility currently has 55 local active users and 35 outside users. To meet the users' needs, we have increased the Resource's computational power by 250% and its total storage capacity by 215%. We have added three new graphics machines, increasing total visualization capability by 25%. For more information see pp. 15.

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

Salih Adem, Bilkent University, Physics Department, Ankara, Turkey (Summer 98);
Emadeddin Tajkhorshid, German Cancer Research Center, Heidelberg University (Fall 1998);
Felix Autenrieth, University of Stuttgart, Department of Biology (October 5 - 12, 1998).

General Services

* The Resource organized a meeting held on March, 3-4, 1999 in Rockville, MD, entitled Opportunities in Molecular Biomedicine in the Era of Teraflop Computing. The conference was sponsored by the NIH/NCRR, and addressed the explosive growth in computational power and biological data bases, and their expected impact on the future of biomedical research. Twenty leading scientists in the field of computational structural biology were invited to discuss relevant research opportunities that will open up with the anticipated increase of computer power, and to elucidate how a state-of-the-art computer facility dedicated to biomedical sciences could facilitate such opportunities. About 50 observers from academic institutions, federal agencies and industry attended the talks and participated in the discussions.

The key issues explored in the meeting included significant research problems that can only be tackled when 100 times more computer power becomes available to individual researchers, and the promise they hold for biomedicine.

The meeting was centered around five themes:

- Simulations of Slow Events
- Combined Classical Quantum Chemical Simulations

- Structure Prediction
- Large Systems
- Role of a National Center for Biological Computing

See Appendix II for the report on the conference.

* The Resource has again organized a highly regarded seminar series in theoretical biophysics with the support of the Beckman Institute and NIH Resource funds. These seminars have become a recognized staple of UIUC campus life, constituting an effective and beneficial tradition for technology transfer and sharing of knowledge with Beckman and other on-campus scientists. During the past year the following outside speakers have presented lectures in the Resource seminar series at the Beckman Institute:

Christopher M. Dobson, University of Oxford, "*The Structural Basis of Protein Folding and Misfolding*."

Alexander Vologodskii, New York University, "*Computer Simulation of Topological Properties of Circular DNAs*."

R. B. Gerber, The Hebrew University of Jerusalem and University of California at Irvine, Irvine, CA, "*Quantum Simulations of Biomolecules: Accurate Potentials from Spectroscopy*."

Benoit Roux, University of Montreal, Canada, "*The Environment of Biomolecules: Atomic and Mean-field Models*."

Graham R. Fleming, University of California at Berkeley and LBNL, "*Femtosecond Nonlinear Spectroscopy Studies of Photosynthetic Light Harvesting*."

Bernard R. Brooks, National Institutes of Health, "*Recent Techniques and approaches for Macromolecular Simulations Requiring High Performance Computing Resources*".

Harry A. Frank, University of Connecticut, Storrs, CT, "*Carotenoids in Photosynthesis: Structure, Spectroscopy and Photochemistry*."

Valerie Daggett, University of Washington, Seattle, WA, "*Towards a Description of Protein Folding/Unfolding at Atomic Resolution*."

Carol B. Post, Purdue University, West Lafayette, IN, "*Insights into Mechanisms of Antiviral Activity and Protein Stability*."

Keith Moffat, University of Chicago, Chicago, IL, "*Nanosecond Time-Resolved X-ray Crystallography*."

Robin Hochstrasser, University of Pennsylvania, Philadelphia, PA, "*Toward the Determination of Peptide Structures by Multidimensional Infrared Spectroscopy*."

Elizabeth Getzhoff, The Scripps Research Institute, "*Resolving Paradoxes in Protein Photocycles at Atomic Resolution: Structural and Mutational Analyses of Photoactive Yellow Protein*."

Daniel Barsky, Lawrence Livermore National Laboratory, Livermore, CA, "*Learning to Recognize Damaged DNA*."

Mehmet Sarikaya, University of Washington, Seattle, WA, "*Biomimetics: Materials Science and Engineering Through Biology*."

Paolo Carloni, International School for Advanced Studies, Condensed Matter Sector, Trieste, Italy, "*Ab initio molecular dynamics studies of targets for anti-AIDS therapy*."

* The Resource has held its annual Open House on December 3, 1998. The yearly event attracts many on-campus visitors, both students and faculty, and leads to renewed and increased interest in our research and development efforts. Close to 100 visitors joined us for tours of the facility and 3D demos.

* The 3D projection facility has been extensively 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. Visitors to the facility over the past grant period included: Dr. Joachim Seelig, Biocenter of the University of Basel, Switzerland; R. Bailey, Illinois State Fair; J. Bredas, Universite de Mons-Hainaut, Belgium; J. Stubbe, MIT; A. Kim, U. of Nebraska; Mr. A. Burnstein, MSI; D. Janezic, National Institute of Chemistry, Slovenia; J. Wooley, U.S. Department of Energy; T. Mattson, Intel; Senators P. Fitzgerald and S. Weaver of Illinois; Paybou, Agricultural Economics; R. Taylor and C. Macrae, CCDC, UK; E. Tajkhorshid, German Cancer Institute; B. Williams, UIUC; C. Dobson, Oxford Centre for Molecular Sciences; B. Hudson, Syracuse University; W. Robinson, Texas Tech U.; J. Katzenellenbogen, Chemistry, UIUC; M. Bailly, CNRS, France; C. Naumann, Stanford; G. Corliss, Marquette University; B. Roux, U. of Montreal; G. Fleming, U. of California, Berkeley; B. Brooks, Computational Research and Technology, NIH; H. Frank, Chemistry, U. of Connecticut; V. Daggett, Medicinal Chemistry, U. of Washington; C. Post, Medicinal Chemistry and Pharmacognosy, Purdue U; K. Moffat, Biochemistry and Molecular Biology, U. of Chicago; R. Hochstrasser, Chemistry, U. of Pennsylvania; E. Getzoff, the Skaggs Institute for Chemical Biology and the Scripps Research Institute; D. Lewis, Director of Mathematical Sciences, National Science Foundation; V. Moy, Physiology and Biophysics, School of Medicine, U. of Miami; A. Roher, Sun Health Research Institute; J. Bucholtz, Chemistry, UIUC; Physics prospective graduate students; Biophysics prospective graduate students.

* At the 1999 Beckman Institute Open House more than 190 visitors came to the VMD demonstrations, which were presented in the 3D visualization facility at the Resource on March 5th and 6th, 1999. The VMD demonstration was voted "Overall Best" by the majority of visitors to the Beckman event.

* Our web server is regularly maintained to give all users of the Internet access to publications, images, and routine activities of the Resource.

Training

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

The Resource organized several events which are reported in the Service and Dissemination sections (meetings, seminars, open house, and more).

The design of on-line and traditional tutorials will receive more attention next year and will become another means of technology transfer. This will increase the dissemination of the Resource's software and methods and the number of users benefiting from them. Specifically, we would like to start in the Fall a new tutorial series to more aggressively disseminate methods and software developed in the Resource to the wider community by senior Resource members.

We will first have the tutorials open to our members and UIUC researchers, and if successful, will develop them further, post on the web and offer them in conferences and professional meetings. Specific subjects that have already been identified for this purpose are: VMD, NAMD, interactive molecular dynamics, molecular replacement, and quantum chemistry. Once the series is established we will again invite outside experts who will strengthen the program even further, by offering workshops on other projects as well.

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

Long and short term visitors to the Resource benefited from on-the-job training and hands-on experience with the software developed and computational expertise residing at the Resource. These included:

Salih Adem, Bilkent University, Physics Department, Ankara, Turkey (Summer 98).
Emadeddin Tajkhorshid, German Cancer Research Center, Heidelberg University (Fall 1998).
Felix Autenrieth, University of Stuttgart, Department of Biology (October 5 - 12, 1998).

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 17 titles including: Nature Structural Biology, Science, Nature, Proteins, Trends in Biochemical Sciences, Folding and Design, Biophysical Journal, Windows, Sys, Journal of NIH Research, MAC world, Linux Journal, C++ Journal, Chronicle of Higher Education, Dr. Dobb's Journal. We expect to continue to purchase books, to keep our journal subscriptions, and possibly add new ones, depending on our research needs and availability of funds. The Resource library is well cataloged. The catalog is available to Resource members on the web (http://www.ks.uiuc.edu/Group/Library/), and the library has become an important training tool for staff members and visitors.

Many of the research and development activities at the Resource are performed by graduate students. The graduate assistants typically leave the Resource once they complete their education. The list below includes M.A. and Ph.D. recipients, postdoctoral associates and undergraduates who received their training at the Resource during the past year.

M.A. Students

1. Krishnan Varadarajan, Computer Science "A Communication Library for Parallel Architectures", May 1999, Software Design Engineer, Microsoft Corp.
2. Parthasarathy Ramachandran, Computer Science "A Parallel Debugger for Converse", May 1999, Siebel Systems, Inc. Software Engineer.

Ph.D. Students

1. Ilya Logunov, Chemical Physics "Molecular Dynamics and Quantum Chemistry Studies of the Protein Bacteriorhodopsin," July 1998.
2. Dorina Kosztin, Chemical Physics "Molecular Dynamics Study of Hormone Receptors Binding DNA and Hormones," November 1998; Postdoctoral Associate, NIH Resource for Macromolecular Modeling and Bioinformatics, UIUC.

3. Sergei Izrailev, Physics "Steered Molecular Dynamics: A Tool to Investigate Molecular Interactions," October 1998; Research Scientist, 3-Dimensional Pharmaceuticals, Inc., Exton, PA.

Postdoctoral Associates

1. Xiche Hu, 1994-98, Assistant Professor, University of Toledo, Toledo, OH.
2. Ferenc Molnar, 1997-1999, Visiting Research Programmer, NIH Resource for Macromolecular Modeling and Bioinformatics, UIUC.

Undergraduate Trainees

1. Katrina Midelfort, University of Illinois, Biophysics, Spring 1998.
2. Adrienne Shapiro, University of Illinois, Physics, Summer 1998.
3. Justin Wozniak, University of Illinois, Computer Science, 1998 – to date.
4. Nicholas Paul Deitz, University of Illinois, Computer Science, 1998 – to date.

- Six new graduate students will be joining the Resource this summer.

Dissemination

The Resource continues to fully utilize the wide array of communication and dissemination tools available today.

The Resource's web site (http://www.ks.uiuc.edu/) represents the group's scientific efforts to the outside world. The site offers scientific, technical and administrative information such as ongoing research projects, main research accomplishments, image and movie galleries, software distributions, publication list with abstracts (and when allowed by publishers, full text), the people in the Resource, 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 600 links to our web pages and it is frequently visited.

A major overhaul of our web site is scheduled for early summer. We intend to use Server Side Includes as our core web management tool and adopt recent technological solutions to renew and rejuvenate the content, format and appearance of the site. AccessWatch Analysis is already in use and offers us a reliable measure of the effectiveness of our web site in generating and meeting community interests (by section). This data is an important resource in guiding the development and maintenance of the site, and is an expression of general trends outside the Resource. Latest figures are presented in a descending order, as determined by the estimated monthly average accesses (based on logs from 4/27/1998 through 4/15/1999):

- General TB Site (http://www.ks.uiuc.edu/) 29,605;
- VMD 10,566;
- NAMD 1,989;
- Papers 991;
- Galleries 687;
- Seminars 338;
- Structural Biology 254.

An access is defined as a request for an HTML page on a given server. We are hoping to identify more reliable measures of visits received on our site in the future. A visit is defined as a unique host active during the period of an hour.

All software manuals and documentation are posted on our web site, as well as images and results of recent work; research and development accomplishments are published in professional journals and are posted on the web; lectures and talks on the Resource activities are given all over the world; various documents such as reports and brochures, are periodically produced and mailed to colleagues, prospective members, and federal offices, as well as 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. A video on Energy Transfer in the Bacterial Photosynthetic Unit has been recently produced for use by NIH officials at the Information Technology for the Twenty-First Century meeting in DC (the video is enclosed with this report). The staff continuously reports key findings and systematically disseminates new knowledge produced by the Resource. A Resource highlight on Simulated Unfolding of a Titin Immunoglobulin-like Domain has been selected to appear in the National Coordination Office's Bluebook FY2000 (http://www.ccic.gov/pubs/blue00/hecc.html). A story on VMD is about to appear in the May issue of "Computer Graphics World" as part of the "Tech Watch" column (http://www.cgw.com/).

The Resource's web site is the principal means of distribution for our software and information on prototype modeling projects and related activities. The components of MDScope, NAMD and VMD, are freely available in source form from the Resource's anonymous ftp site at ftp.ks.uiuc. edu. VMD and NAMD are accompanied by searchable documents: a User's Guide for general users, and a Programmer's Guide for those who want to modify the programs.

A new VMD license has made the registration process more user-friendly and has resulted in more reliable data, improved monitoring of software usage, and a better knowledge of our users' profile and preferences. To determine the number of NIH funded users and assist the agency in its efforts to assess the benefits to NIH sponsored research, users are now required to indicate if their work is NIH-funded. NAMD is already using a registration form and procedure similar to VMD's. A new NAMD license, similar to VMD's, will be adopted soon and will have a further impact on the ease of tracking users' patterns and requirements.

We received 2,022 registrations for VMD 1.2, 1,824 binary downloads, 922 source code downloads, and more than 3,000 reported users. Since VMD 1.3 was released on April 5, 1999, more than 700 users have registered and downloaded the program (as of 4/25/99). Of the 700 registered VMD 1.3 users, close to 25% are NIH supported researchers. NAMD 2.0 has been downloaded 100 times since final release in April, 1999 (as of 4/25/99). Across both programs, roughly 20% of users are funded by NIH and we expect that their share will increase as the software become even more easy-to-use and available on more affordable platforms. Over the last 12 months there have been 900 queries from 350 VMD users and 70 queries from 35 NAMD users. We provide user support through e-mail and the average response time, desired and actual, is 48 hours.

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

- bionet.announce;
- bionet.biology.computational;
- bionet.molec-model;
- bionet.software;
- bionet.software.x-plor;
- chemistry@infomeister.osc.edu;
- beowulf-announce@beowulf.gsfc.nasa.gov;
- comp.sys.sun.announce (VMD only);
- comp.sys.sgi.graphics (VMD only);
- comp.os.linux.announce (VMD only).

* Our VMD brochure (see Appendix III) was totally redesigned last fall and mailed to over 100 research groups around the world. It is also being distributed at all events attended by the Resource members. An updated brochure will be ready for the upcoming Windows release of VMD in the fall of 1999. A brand new NAMD brochure will be produced in the next funding period and will be similarly used.

A new Collaboratory page will soon be established at: www.ks.uiuc.edu/Research/collaboratory.

The images in the Resource image and movie galleries (www.ks.uiuc.edu/Overview/gallery/ and www.ks.uiuc.edu/Overview/movie_gallery/, respectively) represent the main research domains. The collections are continuously updated. Following an extensive review of relevant online galleries outside the Resource, scientific and artistic, a new format is being established and will be available May, 1999.

Finally, during the past year the Resource has published and/or submitted over 40 scientific papers (see pp. 66). The Resource also makes its publications available as preprints and reprints in the form of Technical Reports. The manuscripts are maintained in a database accessible to Internet users and are made available upon request (www.ks.uiuc.edu/Publications/Papers/). When allowed by the publisher, papers are now made available in PDF file format.

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

- May 1998, 83rd Dahlem Workshop on Simplicity and Complexity in Proteins and Nucleic Acids, Berlin, Germany. *From Complexity to Simplicity: How Nature Organizes Light Harvesting in Photosynthesis*.
- May 1998, Innovationskolleg Theoretische Biologie, Humboldt-Universitaet zu Berlin. *From Simplicity to Complexity and Back - The Function, Structure and Mechanism of Light Harvesting Systems in Photosynthetic Bacteria*.
- May-June 1998, 8th International Conference on Retinal Proteins, Awaji Island, Japan. *Quantum Molecular Dynamics Simulations of the Photoprocess in Bacteriorhodopsin*.
- June 1998, Summer School "Structure and Machinery of the Cell," Simon Fraser University, Vancouver, Canada. *Steered Molecular Dynamics*: three lectures.
- June 1998, 10th European Bioenergetics Conference, Goteborg, Sweden. *Molecular Dynamics Studies of Proton Transport.*
- July 1998, Faraday Discussion on "Chemical Reaction Theory" in St. Andrews, Scotland. *The Primary Phototransformation of the Protein Bacteriorhodopsin - an Elementary Reaction with a Precise Initial State in a Well-Defined Cavity*.

- July 1998, Gordon Research Conference on Electronic Processes in Organic Matter, Salve Regina University, Newport, RI. *The Physics of Light Harvesting in Photosynthesis - Excitation Transfer in Hierarchical Aggregates of Chlorophylls and Carotenoids*.
- August 1998, Satellite Meeting of the Budapest meeting on Photosynthesis, Tata, Hungary. *Energy Transfer Between Carotenoids and Bacteriochlorophylls in Light-Harvesting Complex II of Purple Bacteria.*
- August 1998, Biomedical Engineering Seminar Series, Mayo Clinic, Rochester, MN. *Steered Molecular Dynamics Study of Ligand Binding and Strain Sensitivity of Proteins*.
- September 1998, University of Illinois, Theoretical Biophysics Seminar Series. *Steered Molecular Dynamics Studies of Ligand Binding and Protein Unfolding*.
- September 1998, 3rd International Symposium on Biological Physics, Santa Fe, NM. *Steered Molecular Dynamics Studies of Ligand Binding and Protein Unfolding*.
- September 1998, Cultural Night at Lincoln Green, University of Illinois. *Nature's Beauty as Revealed Through its Molecular Machines*.
- October 1998, ISF Workshop "Proton Solvation and Proton Mobility," Neve-Ilan, Israel. *Biophysical Mechanisms of Water-Mediated Proton Conduction and Pumping as Revealed by Two Proteins, Cytochrome c Oxydase and Bacteriorhodopsin*.
- October 1998, Meeting on Protein Dynamic and Function: Light Energy Transduction in Retinal Proteins, The Hebrew University of Jerusalem, Jerusalem, Israel. *What Recent Crystallographic Structures and Classical/Quantum Simulations Tell Us About Bacteriorhodopsin's Photoprocesses and Pump Mechanism*.
- October 1998, Symposium on "Computational Aspects of Protein Folding, The Hebrew University of Jerusalem, Jerusalem, Israel. *How Nature Harvests Sun Light: Modeling Structure and Function of a Multi-Protein Cellular Machine*.
- November 1998, Bar-Ilan University, Department of Physics, Jerusalem, Israel. *How Nature Harvests Sun Light*.
- November 1998, Seminar at The Hebrew University of Jerusalem, Jerusalem, Israel. *Atomic Force Microscopy and Steered Molecular Dynamics Studies of Protein Stretching and Unfolding*.
- November 1998, Seminar at the Hebrew University of Jerusalem, Jerusalem, Israel. *Protein Folding and Aggregation/Structure Prediction, Structure Determination, and Mechanism of Light Harvesting Proteins in Purple Bacteria*.
- December 1998, 17th International Meeting of the Molecular Graphics and Modeling Society, San Diego, CA. *Manipulating Proteins by Steered Molecular Dynamics*.
- January 1999, AAAS Annual Meeting, Anaheim, CA. *How Nature Harvests Sun Light*.
- March 1999, Workshop on Opportunities in Molecular Biomedicine in the Era of Teraflop Computing, Rockville, MD. *Molecular Biomedicine in the Era of Teraflop Computing - Opportunities Ahead*.
- March 1999, Beckman Institute Director's Seminar Series, University of Illinois. *How Nature Harvests Sun Light*.
- April 1999, European Workshop on Electronic and Structural Dynamics of Light-induced Processes in Bacteriorhodopsin, University of Lausanne, Switzerland. *Quantum mechanical description of the picosecond photoprocess initiating proton pumping in the protein bacteriorhodopsin*.
- April 1999, Lecture at Cornell University, Ithaca, NY. *Steered Molecular Dynamics to Study Biopolymer Association and Stretching*.
- May 1999, Lecture at Kansas University, Lawrence, KS. *Molecular Biomedicine in the Era of Teraflop Computing - Opportunities Ahead*.

- May 1999, Lecture at the University of Michigan, Ann Arbor, MI. *Life "in silico"*.
- May 1999, International Symposium, "The Treatment of Complex Chemical Systems: New Concepts in Theory and Experiment", Darmstadt, Germany. *Steered Molecular Dynamics to Study Biopolymer Association and Stretching*.

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

- Appointment and Promotions Committee, Physics Department, UIUC;
- Ph.D. Qualifying Exam (August 30-31, 1999), Physics Department, UIUC;
- Biotechnology Faculty Advisory Committee member, UIUC;
- Biotechnology Council Member, UIUC;
- Advisory committee of the NIH Resource at Cornell University;

- Reviewer for the Journal of Physical Chemistry; Biophysical Journal; Journal of Chemical Physics; National Institutes of Health; National Science Foundation; International Journal of Quantum Chemistry; Biochimica et Biophysica Acta; Science; American Chemical Society; UIUC Campus Research Board; Proceedings of the National Academy of Sciences; Proteins, Structure, Function, and Genetics; Journal of Computational Physics; Europhysics Letters; Journal of Computational Chemistry; Journal of Molecular Biology; Human Frontier Science Program Organization; Journal of Theoretical Biology; Federation of European Biochemical Societies Letters; Nucleic Acids Research; The Israel Science Foundation.

In the past year the PI was a Fellow of The Hebrew University of Jerusalem, October 1998 – January 1999.

During the past year research personnel of the Resource have participated and/or presented contributions at the following meetings and institutions:

- Mathematical Sciences Research Institute Workshop, Berkeley, CA, Christian Forst.
- Gordon Conference on Biopolymers, Newport, Rhode Island, Hui Lu.
- International conference on Intelligent Systems for Molecular Biology, Montreal, Canada, Christian Forst.
- Methods and Applications of Molecular Mechanics and dynamics to Molecules of Biological Interest, Pittsburgh, PA, James Phillips and Dorina Kosztin.
- International Workshop on Light Harvesting Systems, Tata, Hungary, Thorsten Ritz and Ana Damjanovic.
- 11th International Congress of Photosynthesis, Budapest, Hungary, Thorsten Ritz.
- Cell and Molecular Biology and Molecular Biophysics Research Symposium, Beckman Institute, UIUC, Urbana, IL, Alexander Balaeff, Ana Damjanovic, Cristian Forst, and Barry Israelewitz.
- MVD ACM/SIGGRAPH, University of Missouri at Rolla, MO, John Stone.
- SuperComputing '98, Orlando, FL, James Phillips.
- Molecular Modeling in the Large, San Diego, CA, Barry Israelewitz, Hui Lu and Ferenc Molnar.
- ISCOPE '98, Santa Fe, NM, Robert Brunner and James Phillips.
- SIAM '98, New York, NY, Laxmikant Kale and James Phillips.
- Irregular '98 conference, San Francisco, CA, Laxmikant Kale.
- Conference on Parallel Object-oriented Computing, Santa Fe, NM, James Phillips.

- International Conference on Web-based Modeling and Simulation, San Francisco, CA, James Phillips.
- 43rd Biophysical Society meeting, Baltimore, MD, Thorsten Ritz, Barry Isralewitz, Ferenc Molnar, Hui Lu, Jerome Baudry, and Ana Damjanovic.
- Frontiers '99 conference, IEEE, Annapolis, MD, Robert Brunner.
- Workshop on Opportunities in Molecular Biomedicine in the Era of Teraflop Computing, Rockville, MD, Gila Budescu, Robert Skeel, Laxmikant Kale, Ferenc Molnar, Justin Gullingsrud, Barry Isralewitz, Jerome Baudry, Hui Lu, Dorina Kosztin, and James Phillips.
- IPPS-SPDP'99, San Juan, Puerto Rico, L. Kale.
- RECOMB'99, Lyon, France, Christian Forst.
- 5th SIAM Conference on Applications of Dynamical Systems, Snowbird, Utah, Robert Skeel.
- EPSRC Numerical Analysis Summer School '98, Leicester, England, R. Skeel.
- Faraday Discussion meetings, St. Andrews, Scotland, Todd J. Martinez.
- *Ab Initio Quantum Photodynamics: New Twists on cis-trans Photoisomerization*, University of Iowa, Todd J. Martinez.
- *Ab Initio Molecular Dynamics of cis-trans Isomerization*, 5th Symposium on Molecular Reaction Dynamics in Condensed Matter, Newport Beach, CA, Todd J. Martinez.
- *Structure and Dynamics of Electronic Excited States: From Triatomics to Proteins*, Northwestern University, Todd J. Martinez.
- *Ab Initio Molecular Dynamics with Quantum Effects*, CCP1 Study Weekend, Daresbury Laboratory, Daresbury, United Kingdom, Todd J. Martinez
- *First-Principles Photochemistry: From Triatomics to Proteins*, University of Chicago, Todd J. Martinez.

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