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Principal Investigator:	
Klaus Schulten, PhD	

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Signed:	May 15, 1995
Telephone Number:	(217) 244-2212
Facsimile Number:	(217) 244-6078
Electronic Mail Address:	kschulte@ks.uiuc.edu

Summary of Research Progress

This progress report covers the fifth year of an eight year period of funding for the Resource. The past year has been characterized by a major milestone for our Resource with the completion and the initial public distribution of the software package `MDScope`, an interactive modelling package for structural biology developed by members of the Resource. The year has also seen a great increase in the depth and breadth of collaborative projects with on-campus and off-campus molecular biology laboratories.

The completion of `MDScope` is an important event. Molecular dynamics (MD) simulations are playing an increasingly important role in the study of structure and function of biomolecular systems and in rational drug design. MD simulations have been applied to the refinement of structures derived from X-ray diffraction and NMR data, to the investigation of enzymatic mechanisms and enzyme inhibitors, to the study of biopolymer aggregates like membranes, and the prediction of protein structure. Unfortunately, MD simulations are computer time-intensive and simulations currently require several hours or days to complete.

If MD simulations could be computed sufficiently fast, exciting interactive applications in structure refinement, structure prediction and drug design would become feasible since simulations could involve direct feedback from users. For this purpose, a researcher would need to have immediate access to the results of MD simulations through a suitable molecular graphics user interface. Such interaction would require a certain level of computational and display performance, i.e., 100 femtoseconds (fs) of motion for a protein with 1,000 atoms would need to be computed and visualized within 10 seconds. The program `MDScope` for interactive simulation of biopolymers takes an important step toward this goal.

The primary performance barrier to achieving interactive MD is the speed at which MD simulations can be calculated. Available network technologies are able to transfer MD trajectory data at a sufficient rate to allow interactive MD. Further, current computer graphic systems are able to render images fast enough to support real–time motion. It is possible to overcome the performance barrier by using the full capabilities of high–performance parallel computing platforms. This in turn, requires a molecular dynamics program which runs efficiently on such platforms and which is well integrated with a molecular graphics package.

The Resource's computer system together with `MDScope` provides such an environment. The program combines (1) the molecular visualization program `vmd` for interactive display of molecular systems, (2) the molecular dynamics program `namd` expressly designed for efficient execution on parallel computer platforms, and (3) a protocol and library `MDComm` which functions as a communication agent between `vmd` and `namd`. The programs `vmd`

and namd are described in two of the Research Highlights of this Report. MDComm has been developed jointly with the National Center for Supercomputing Applications.

The program MDScope together with a detailed programmers guide have been recently made available to the biomedical research community; the Resource will release a users manual in the near future. The programs are written in an objective oriented style using the language C++; this design and the ample documentation will allow researchers to add to the program and modify it for their needs. The program is already employed by the two biocomputational Resources in North Carolina. We expect that MDScope will have a strong impact on computational structural biology since it combines three major technological advances. namd is the first molecular dynamics program which has been designed specifically for parallel computers, vmd is the first interactive molecular graphics program which allows the use of three-dimensional input devices, and finally a speech recognition interface is also being implemented. Both namd and vmd surmount the barrier to program modifications for other researchers, since the programs constitute a library of well documented routines. This library is made available in source code and can be readily altered and extended by the biomedical research community.

This is the second year of deployment for the Resource's main computational platform, a cluster of high performance workstations coupled through a fiber optic switch. The cluster has proven to be a good choice for many reasons. Growing commercial demand for systems such as ours is reducing the costs of the necessary components and spurring very rapid improvements in performance. Therefore, solutions developed by the Resource will be able to be utilized by the research community at large in the near future. The computer system has also proven to be very cost effective and versatile. It continues to provide the computing capability for research projects which could not be undertaken otherwise, even with the renewal of a large allocation of computer time from the NSF Supercomputer Centers that the Resource was awarded this year. Naturally, the Resource cluster continued to develop during the past year achieving a better balance between computational and data storage capabilities. One workstation has been configured as a quantum chemistry machine to serve respective needs which have experienced a sharp rise at the Resource.

A second significant development was the addition of eight new collaborations to investigate: protein folding, bioenergetic proteins like the bc1 complex and the light harvesting system, protein-DNA complexes involving gene V protein, the estrogen receptor and high mobility group proteins, immobilized artificial membranes used for drug assays, G-actin polymerizing into muscle filaments, and the coat proteins of polio virus. These collaborations received funding through a private Foundation, the Roy J. Carver Charitable Trust. Some of the projects have already reached fruition and are described below. The majority of the projects are expected to mature during the coming two years. The collab-

orations are an extremely important activity that bridges the gap between experimental laboratories and the Resource's computer laboratory. We hope to demonstrate, through several important research problems, the value of computational methods for molecular biology and medicinal chemistry.

The Resource organized a one week training workshop on molecular dynamics during the past year which provided lectures and hands-on experience in extended laboratory sessions. The lecturers were Jan Hermans and Ken Flurchick from the North Carolina Supercomputer Center. The Resource also participated in coordinating a very successful one week workshop on molecular biology held during the summer at the Institute for Mathematics and its Applications at the University of Minnesota. Both workshops were attended by student, post doctoral and senior researchers.

Finally, the extended documentation of the Resource program `MDScope` is expect to serve an important role in the training of the biomedical research community in the use of biomolecular modelling programs.

HP Workstation Cluster

The workstation cluster, configured and installed by the Resource, is a prototype for the class of computational environment we expect will be used by biomedical research laboratories in the near future. This environment will interconnect increasingly powerful and cost-effective scientific workstations through high speed fiber optic links and switches which, like a modern telephone network, provide dedicated lines of data transfer between any pair of workstations.

The Resource's workstation cluster provides a testbed for this development. It utilizes Hewlett-Packard (HP) workstations and a fiber-optic network switch based on the emerging ATM (asynchronous transfer mode) technology, a technology which is also used by the National Research Network (NREN). Our programs for biomedical research are developed and tuned specifically for such computational environments and we expect that this experience and our specific programs will benefit NIH researchers in the near future. An example is the development of the program package `MDScope` which connects a new molecular graphics system (`vmd`) with a simulation program `namd` running on separate machines in a cluster (see the `namd` and `vmd` highlight sections in this report).

The use of the ATM technology allows one to turn a workstation cluster into an efficient parallel computer. In collaboration with A. Brünger at Yale, this was demonstrated by Parallel X-PLOR, a parallel processing version of the widely used modelling program X-PLOR in collaboration with A. Brunger at Yale. Figure 1 illustrates the improvement gained through the use of ATM compared to the use of the current Ethernet technology. The cluster successfully runs other modelling programs, e.g., X-PLOR, CHARMm, Parallel CHARMm, as well as the modelling programs PMD and `namd` developed by Resource researchers. These programs are used routinely by our researchers and collaborators on the Resource cluster. Furthermore, through the use of parallel programming languages, such as the one developed by co-PI L.V. Kale, highly portable parallel programs can be developed to be used on machines ranging from the workstation cluster to massively parallel computers, including those at the National Supercomputer Centers. The Resource has been awarded an NSF Meta-Center Allocation award to use various massively parallel machines, and is porting its programs to these machines.

The Resource cluster has continued to evolve since its original installation in November 1993. The development is the result of the need to balance all components of our computational environment: fast processors, high speed communication links, short term and long term (archival) storage systems. Presently, the cluster consists of 14 HP 9000-735/125 workstations, of which twelve are interconnected by a Fore Systems ATM switch utilizing 100 megabit/second fiber-optic ports. Additionally, these systems have been augmented by a newly acquired central HP 9000/800-E25 file server with 12 gigabytes (GB) of disk, a 20 GB optical disk juke box for archival storage and extra disk drives

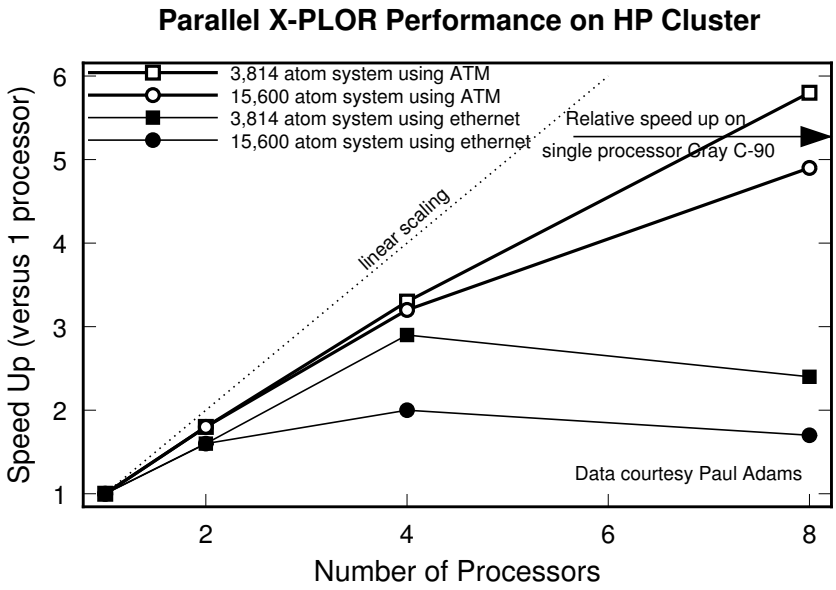

Figure 1: Speedup of Parallel X-PLOR for a simulation of a 3,814 and a 15,600 atom system on the Resource's workstation cluster utilizing the ATM network or the ethernet network. The relative speed for both systems on a single processor Cray C-90 is marked for reference. Data courtesy Paul Adams, Yale University.

for the cluster machines, including two fast 8 GB disk systems. One cluster machine has been especially tailored with large and fast disk drives for quantum chemical calculations for biomolecules. In all, the cluster has access to about 50 GB of disk space.

Molecular Modeling: The Program `namd`

The Resource has recently developed `namd`, a parallel molecular dynamics program designed for high-performance simulations in structural biology. This program is intended for structural biologists, in particular, those who employ large-scale molecular dynamics simulations or are interested in testing novel simulation methods. The major goals for `namd` are high performance and scalability. In addition, `namd` is highly modular and well documented to facilitate the addition of new algorithms and methods.

Currently, distributed memory parallel computers offer cost-effective high performance computing and scalability. Therefore, `namd` was written expressly for these machines. The program `namd` utilizes a message driven, multithreaded design to provide high performance that is tolerant of communication latency. While `namd` is a recent development and many performance improvements are still being implemented, we have already obtained encouraging results running the program on our cluster of HP workstations. The performance of `namd` on a system of about 10,000 atoms is shown in Figure 2.

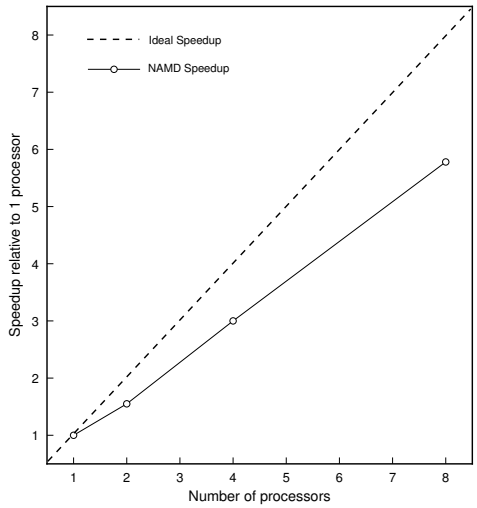

Figure 2: Speedup of `namd` for a simulation of a $10,000$ atom system on the cluster of HP workstations within the Resource.

The program `namd` is designed to perform MD simulations of biopolymer systems ranging in size from thousands of atoms to millions of atoms, and to be executed on parallel computers ranging in size from tens of processors to thousands of processors. To accommodate these ranges, `namd` must scale efficiently with the size of the simulated biopolymer system as well as with the number of processors, and it must insure scalability in communication and memory usage. To achieve this goal, `namd` uses spatial decomposition to divide the work among processors.

An example of a spatial decomposition displayed using the graphics program `vmd` written by Resource staff is shown in Figure 3. By using a spatial decomposition scheme, the

computation, memory, and communication required for each processor scales as $O(N/P)$ where N is the number of atoms and P is the number of processors. Thus, `namd` can scale efficiently to simulate the largest systems using computers consisting of hundreds of processors.

The modular design of `namd` facilitates the evaluation of algorithms derived from new physical concepts in a simple and flexible manner. For many calculations of interest, faster hardware, even with massive parallelism, would be insufficient, and only new algorithms will make these simulations feasible. Attaining the highest performance through the use of these new algorithms requires continuous adaptation of the program. To achieve this flexibility, `namd` uses an object-oriented design and is implemented in C++. Such an implementation provides a high degree of modularity and data abstraction, making the program easy to modify and maintain.

To enhance the ability to modify and maintain the program, `namd` has been fully documented in a *Programmer's Guide*. This document provides a complete description of the design and implementation of the program, including a detailed description of the algorithms used. A principal objective of this guide is to allow researchers to understand the program without resorting to examination of the source code. It also permits researchers to quickly determine how to add new algorithms to the program.

One of the important features of `namd` is the inclusion of full electrostatic interactions. Most MD programs truncate electrostatics to reduce the computational complexity of directly computing interactions between all pairs of atoms. However, this type of truncation has been demonstrated to lead to qualitatively wrong descriptions of physical properties. The program `namd` has incorporated the Distributed Parallel Multiple Tree Algorithm (DPMTA) [1] developed by our collaborators at Duke University. This algorithm reduces the computational complexity of computing the electrostatic electrostatic interaction between all pairs of atoms from $O(N^2)$ to $O(N)$. Combined with a multiple timestep integration scheme, this allows `namd` to include full electrostatics without incurring an enormous computational cost.

As one of three components of the MDScope system [2], `namd` communicates with `vmd` using the `MDComm` software. This interaction allows a user to employ `vmd` as a graphical console which can start `namd`, view, and modify the simulation to some extent. The communication between `namd` and `vmd` is being enhanced to permit greater interaction between the user and the molecular dynamics simulation.

The program `namd` is currently available for HP, SGI and IBM workstations as well as the Convex Exemplar, with versions for more machines expected shortly. The source code and documentation for `namd` are publicly available via anonymous ftp from `ftp.ks.uiuc.edu` in the directory `/pub/mdscope/namd`.

Molecular Visualization: The Program `vmd`

In the past year, the Resource has been developing an extensive problem-solving environment for molecular dynamics and modelling studies in structural biology, known as `MDScope` [2]. This environment consists of a visualization component (the program `vmd`), a molecular dynamics simulation component (the program `namd`, described previously in this report), and a library to allow these programs to communicate efficiently between different computers (the `MDComm` library). The program `vmd`, the interactive visualization component, is used on a graphical workstation to display molecular structures which can be manipulated in a variety of manners, for example, through the use of a mouse in conjunction with a graphical user interface, or through commands entered through the keyboard. At the same time, `vmd` can communicate with `namd`, the component of `MDScope` which computes the dynamical motion of a molecule, and visualize the results of the calculation as it is computed. The program `vmd` acts as a controlling interface to `namd`, allowing a person to interactively start a new molecular dynamics simulation, and then view and modify the results.

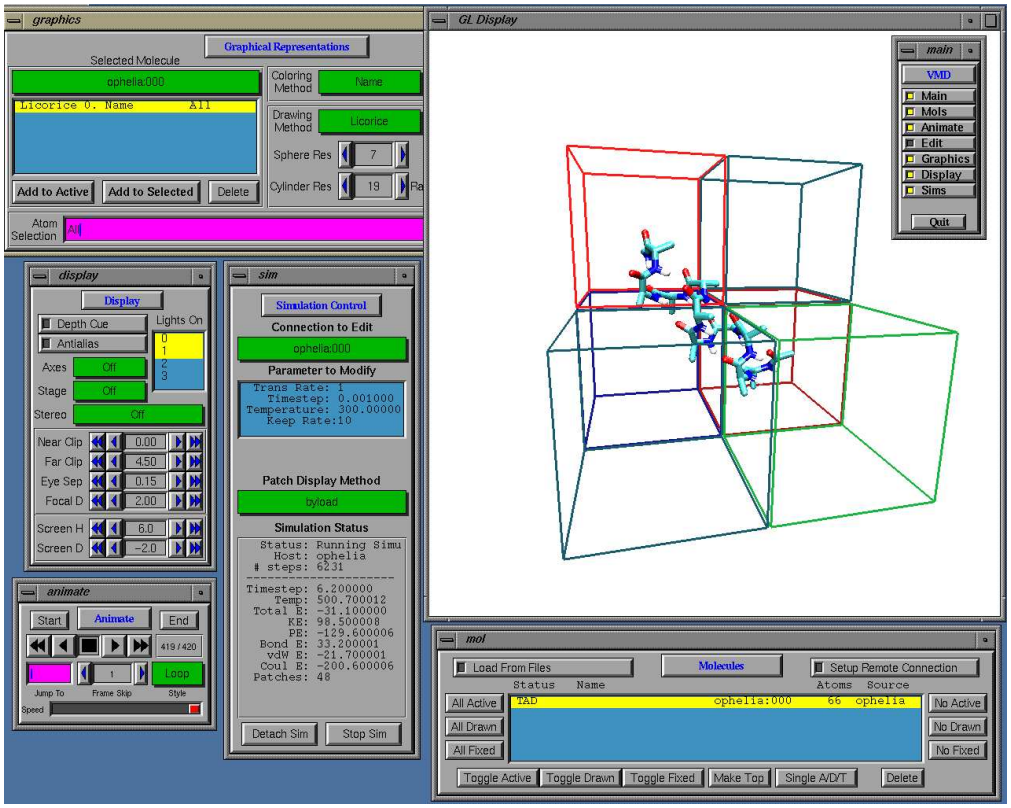

Figure 3: Sample `vmd` session. The boxes surrounding the protein in the display window visualize the spatial decomposition used in the parallelization strategy of the program `namd`.

One of the key functions of the program `vmd` is visualization of molecular systems, in particular, biological molecules such as proteins, nucleic acids, or membranes. To achieve

this objective `vmd` provides a wide variety of methods for rendering and coloring the structure – simple lines, CPK spheres, licorice bonds, and other representations. The display of molecules in `vmd` is achieved by means of user-configurable *representations* of each molecule. These representations are displayed simultaneously, each consisting of a subset of atoms, and a particular method for rendering and coloring the atoms and bonds selected.

The program `vmd` has been developed with the capability to use a number of different graphical display and input devices, in order to provide the viewer with a realistic three-dimensional working environment. An example of a particularly useful three-dimensional display and input system, described in the previous year's progress report, is a large-screen projector capable of displaying stereo video images produced by a graphics workstation. This display is coupled with a spatial tracking device which can measure the 3D position and orientation of a sensor relative to some fixed emitter. With this system, several people can perceive themselves occupying the same space as the molecule.

The goal of `MDScope` is to facilitate direct interaction between researchers and molecules which are simulated on supercomputers or the Resource's workstation cluster. The program `vmd` supplies the "front end" to this process and uses the `MDComm` library to communicate with the simulation program. The program `vmd` may be used to start up new `namd` simulations on either the same computer running `vmd` or on a different computer, and can be further used to view the motion of the molecule as it is being calculated. One can start up an `namd` job with `vmd`, and then *detach* from it, leaving the job running independent of `vmd`. Later, one may reconnect to the same detached job, and resume display of the simulation. Figure 3 illustrates the use of `vmd` for visualization and control of an `namd` simulation.

All the features described here have already been implemented and made available for use on Silicon Graphics workstations. We are at present expanding `vmd` to include the ability to add user-selected forces to a specific atom or group of atoms in a simulated molecule, which will be sent back to `namd` and incorporated into the simulation directly. This feature would be useful, for example, for interactive placement or refinement of the positions of ions or water molecules within a biopolymer. Thus, one may interactively apply forces to certain atoms in order to move components of the molecule to a desired location, and the atoms would respond by moving along the pathway allowed by the surrounding atoms. This would also allow the surrounding atoms to rearrange their positions in a consistent manner as the other atoms are moved. The program `vmd`, with documentation and complete source code (in C++, an object-oriented extension of the C programming language), is freely available for researchers from the anonymous ftp server `ftp.ks.uiuc.edu`, in the directory `/pub/mdscope/vmd`.

Molecular dynamics simulation of an Immobilized Artificial Membrane

In collaboration with Charles Pidgeon at Purdue University, the resource has performed molecular dynamics simulations for immobilized artificial membrane (IAM) [3] and IAM–solute systems. IAMs are stable models of fluid membranes that can be used to rapidly evaluate drug-membrane interactions [4], and to purify proteins which bind to membrane surfaces [5, 6]. IAMs are prepared from lipid analogs, including double chain ester phosphatidylcholine (PC) analogs covalently attached to silicon surfaces. The chemical components and the chemical attachment of IAM differ from biological fluid membranes, thus, the ability of the IAMs to predict drug–membrane interactions was surprising. This discovery implies that some physical-chemical properties of IAMs must be similar to that of fluid membranes.

Following previous studies of membrane bilayers [7, 8], a molecular dynamics simulation was recently performed for a IAM-PC membrane [3]. The goal of the calculation was to compare the structure and dynamics of IAM to fluid membranes. The IAM was constructed based on experimental data provided by Pidgeon's group [9] and the simulation was carried out using the program X-PLOR on the Hewlett-Packard workstation cluster of the Resource. The simulation required approximately one month on a single Hewlett-Packard workstation.

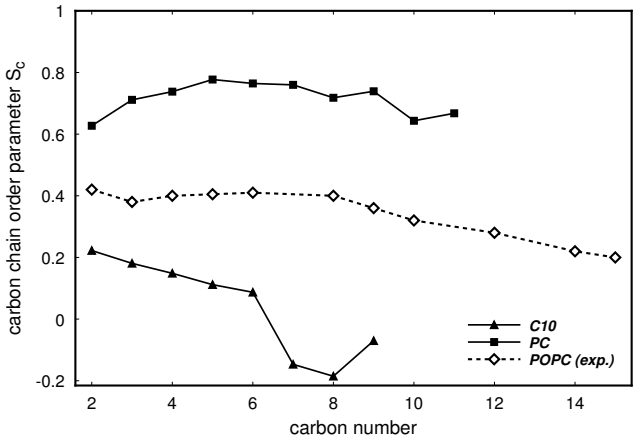

Figure 4: Order parameters of the lipid hydrocarbon chains (solid squares) and C10 molecules (solid triangles) calculated from the simulation of IAM-PC. The experimentally measured order parameters for hydrocarbon chains of the DPPC membrane are shown for comparison (open diamonds). The order parameters measure the orientational disorder of the lipid molecules in the membrane.

The IAM surface simulated contained 36 PC molecules and 10 C10 molecules according to the experimental conditions and was simulated with a water layer containing 2487 water molecules. The simulation was carried out for 250 ps. The distribution of membrane

head groups, glycerol backbones as well as hydrocarbon tails were analyzed and found to be very similar to the corresponding properties of a fluid membrane bilayer. The hydrocarbon tails of IAM were found to be more ordered than in a fluid membrane (see Figure 4). Water molecules were found to be polarized in the interfacial region, the polarization decaying exponentially into the bulk water region with a decay length of 13 Å. The dynamics of the lipid hydrocarbon tails and head groups was found to be in agreement with experimental measurements. The simulation results suggest that large cavities are formed in IAMs which might resemble the dynamic defect structures formed in a fluid membrane. Similarities observed for the IAM and fluid membranes through MD simulation explain, in part, why IAMs can be experimentally used to measure membrane partition coefficients for drugs and solutes. The models obtained from present simulations also offer a starting point for future studies of drug–membrane interactions.

Following the studies of the IAM-PC membrane, a simulation was carried out for the IAM-PE membrane. The simulation revealed many characteristics of IAM-PE which are similar to that of IAM-PC, such as clustering of the head groups, hydrogen bonding between the amino and carbonyl groups of the lipid analogs in the region close to the silicon surface. These results are in agreement with previous experimental studies.

Experimental measurements on the free energy changes associated with the partitioning of bile salts into IAM were previously made for a large number of bile salts [10]. Accordingly, simulations of IAM-PE interacting with three different bile salt molecules were performed using the equilibrated IAM-PE membrane. Enthalpy changes experienced by these three compounds, when transported from water to the IAM surface, were obtained from these simulations, and show the same order for the three bile salt molecules as the experimentally measured partition free energy changes. Even though a quantitative agreement still requires more accurate calculations, the results are encouraging and suggest that the current IAM models are useful in studying drug partitioning in membranes. Future experimental and theoretical investigations of the IAM-solute interactions might assist the prediction of drug transport properties across biological membranes and help the evaluation of drug bio-availabilities.

Molecular dynamics studies of the phospholipase A_2–membrane complexes

Phospholipase A_2 (PLA_2), which catalyzes the hydrolysis reaction of the *sn*-2 ester bond of phospholipid [11, 12], plays an important physiological role and has been investigated by many researchers during the last 30 years. One of the reaction products of PLA_2, arachdonic acid, is an important metabolic intermediate for producing eicosanoids, which are regulatory factors implicated in a wide range of physiological and pathological states such as inflammation, asthma, ischaemia, toxic shock, burn trauma, pancreatitis and rheumatoid arthritis [13, 14]. The enzyme has been studied extensively using biochemical methods, and significant efforts have been made in designing potent inhibitors for it.

Initiated as a collaboration with the Eli Lilly pharmaceutical company, a modelling study of human synovial phospholipase A_2 was carried out employing the Resource cluster and the Resource modelling software. The project focused on understanding of the interactions between the protein and the membrane, as well as on the functional significance of such interactions.

Human synovial phospholipase A_2 is the extracellular PLA_2 found in the synovial fluid of arthritis patients [15, 16]. The kinetics of the enzyme has been studied by a few groups and recently on DMPM lipids by Jain's group [17]. The structure of the enzyme in solution and of the enzyme binding a inhibitor has been reported [18, 19]. The enzyme phospholipase A_2 displays a much higher activity when tightly associated with lipid aggregates, such as micelles or lipid bilayers, compared to the enzyme acting on lipid monomers in aqueous solution [20, 21]. Various models have been suggested to explain such activation phenomenon. The studies carried out at the Resource were intended to examine the mechanism of the enzyme surface activation.

Two PLA_2–membrane complexes were studied based on experimental suggestions, namely PLA_2 loosely and tightly bound to the membrane surface. Simulations of 140 ps each were carried out for these two complexes and for PLA_2 in water using the program PMD [22]. These calculations required a total of 3 month calculation time on the Resource cluster. Free energy calculations of the lipid head group solvation were performed in parallel using four single workstations.

A desolvation of lipid molecules in a tight protein–membrane complex was previously suggested by experiment [23]. The calculations carried out by us are in agreement with this suggestion and show that lipids interacting with protein hydrophobic residues are indeed desolvated, the calculated desolvation energy measuring 7–8 kcal/mol per lipid. These lipid molecules, which are located close to the entrance of the enzyme active site, are destabilized energetically and, therefore, should diffuse into the active site at a higher rate, resulting in the enhancement of enzyme activity. Also in agreement with experimental

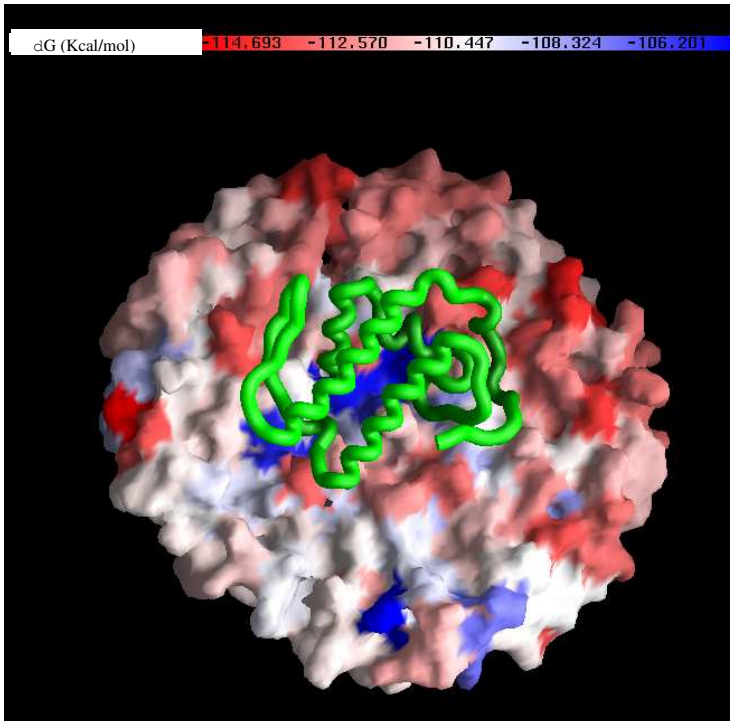

Figure 5: Desolvation effect in the tightly bound PLA_2–membrane complex. Desolvated, *i.e.*, energetically destabilized, lipid molecules are shown in blue; these molecules interact mostly with hydrophobic protein residues near the entrance to the active site of PLA_2.

evidence, the calculated desolvation effect is not observed for the loosely bound protein–membrane complex. These results explain partly why the proenzyme PLA_2, well known for its incompetence to bind tightly on membrane surfaces, retains prefect function for lipid monomers in solution, but does not exhibit activation on membrane surfaces.

Human synovial PLA_2 is known to have a high affinity for negatively charged membrane surfaces. The dependence of enzyme affinity on membrane surface charges were also investigated by the Resource and qualitative agreements are obtained with experiments [24]. Predictions are made for residues important for the charge–charge interaction between protein and membrane which may be tested by future mutation studies.

Molecular Dynamics Study of the M Intermediate of Bacteriorhodopsin – Collaboration with M. Sheves, Weizmann Institute

Bacteriorhodopsin (bR), a retinal protein in the purple membrane of *Halobacterium halobium*, functions as a light-driven proton pump. The protein generates an electrochemical potential gradient across the cell membrane, which is utilized for ATP synthesis. The study of bR yields a better understanding of membrane proteins, photochemical transformations, bioenergetics and the vision process.

Bacteriorhodopsin transfers protons from the cytoplasmic to the extracellular side of the cell membrane through a cyclic process initiated by absorption of a photon. This photon triggers an isomerization of a retinal molecule bound via a Schiff base linkage to Lys-216 of bR, which proceeds through several intermediate states characterized by isomeric, protonation and spectral changes. The M state is a key intermediate during which the retinal Schiff base nitrogen moves from a proton transfer contact with the extracellular side to a contact with the intracellular side.

The times for the formation and decay of the M intermediate are in the μs and ms range; presently, computational resources allow one to cover in molecular dynamics simulations time periods of a few nanoseconds at best. Starting from the refined structure of bR described in [25], we employed a suitable simulated annealing schedule [26], which accelerated the reaction processes and allowed us to generate the M state. The simulations were carried out with X-PLOR on Silicon Graphics and Hewlett-Packard workstations at the Resource.

Our simulations revealed a very heterogeneous M intermediate. Seven substates were consecutively generated in the simulated annealing protocol during the M stage. The simulations indicate that M should be considered a sequence of states, i. e., a process, rather than one distinct state. This result supports observations that M consists actually of more than one state [27, 28, 29].

In the counterion region and in the extracellular channel, three water molecules arranged themselves to connect to the hydroxyl group of Tyr-57 and to the oxygen of the Thr-89 hydroxyl moiety as shown in Figure 6. The hydroxyl groups of these waters, which are involved in the hydrogen bonding chain between the waters themselves, lie approximately along a line, and the planes of these waters are nearly parallel. The hydroxyl group of Aps-85, the group to which the Schiff base transfers a proton upon M formation, lies almost perpendicular to this water plane. As a result, Asp-85 is not interacting with the surrounding waters. This result is consistent with FTIR measurements reported in [30] which indicate that Asp-85 is in a hydrophobic environment at the M stage. The lack of

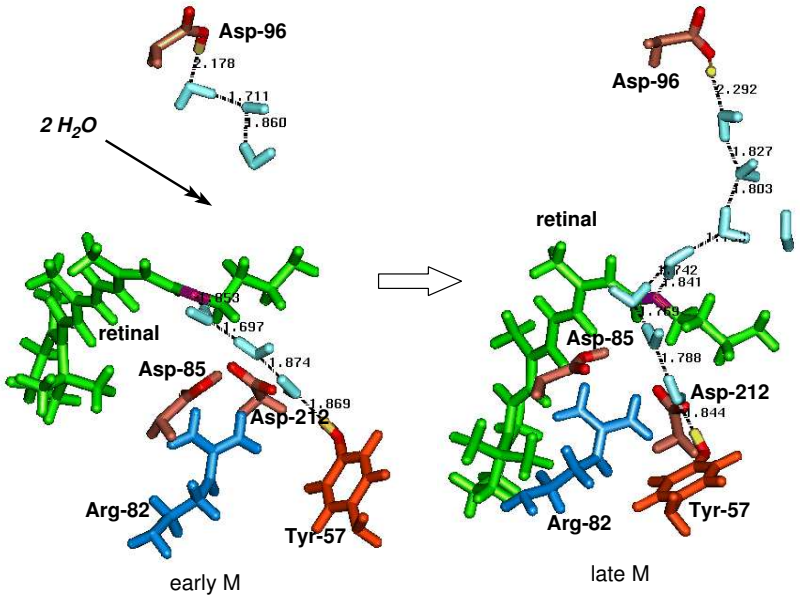

Figure 6: Structure of early M and late M, with retinal and water acting as proton switch.

hydrogen bonding between water and Asp-85 can also explain how the back-transfer of the proton from Asp-85 to retinal is prevented.

We observed the movements of α-helical segments upon formation of the M state, in particular, a large bend of helix F of about 60° away from the center of bR similar to that reported in [31]. This bend opens the cytoplasmic channel of bR and allows access of more waters. Concomitant with the bend of helix F the ring of Tyr-185, on the extracellular side of this helix, moved by about 3.8 Å away from the Schiff base towards the extracellular side and towards the ring region of retinal. This significant motion is due to a weakening of the interaction of Tyr-185 with the hydrogen bond network of waters through proton transfer from retinal to Asp-85. Our findings are in agreement with [32].

The conformational change of helix F introduced cavities in the cytoplasmic channel which provide space for more water molecules. Accordingly, we placed two waters (see Figure 6) during our simulated annealing protocol. Consequently, a water at the cytoplasmic side moved towards the Schiff base and the Schiff base rotated towards the cytoplasmic direction, to finally hydrogen-bond with this water. This move lead to a breaking of the hydrogen bond between the Schiff base and the water at the extracellular side, and formation of hydrogen bonds between waters in the cytoplasmic channel and in the counterion region. This placement resulted in the late M demonstrated in Figure 6 which formed the desired hydrogen bond network between Asp-96, Thr-46, Phe-219, Lys-216 and the Schiff base. Figure 6 also shows how water molecules disconnect their hydrogen bond network from Asp-85 and establish a network between Asp-96 and retinal, the M intermediate thereby realizing its function of a protein switch.

Models of Orientation and Ocular Dominance Columns in the Visual Cortex: A Critical Comparison

In extension of a collaboration with G. Blasdel at Harvard University, this project focuses on a critical comparison between recent experimental data and theoretical models of the visual cortex. Only by implementing the computational models on a parallel supercomputer, a CM-5 Connection Machine at the National Center for Supercomputing Applications (NCSA), was it possible to address the complex map formation process in the visual cortex while using biologically plausible paradigms.

Many cells in the mammalian primary visual cortex are binocular, responding better to stimulation of one eye over the other. They also usually respond more strongly to bars or gratings of one particular orientation [33, 34]. Early experiments with microelectrodes revealed a vertical organization, with columns of cells with similar properties running between pia and white matter, perpendicular to the cortical surface. These experiments also revealed a lateral organization characterized by mostly smooth changes in response properties with lateral distance.

In recent years, imaging techniques [35, 37, 38, 39] have been developed which allow an increasingly improved characterization of striate cortex organization and a refined picture of map organization has emerged [35, 37, 36, 40].

Along with the study of cortical organization came a series of experiments suggesting that important elements of the organization of orientation and ocular dominance in macaque striate cortex are not prespecified, but emerge during an activity-driven, self-organizing process. Occlusion of one eye, for example, leads to dramatic changes in the lateral organization of ocular dominance, which are to some extent reversible. Strabismus leads to changes in the degree of binocularity. Exposure to a restricted set of orientations causes changes in the distribution of cells with different preferred orientations. See [41, 42, 43] for reviews. These findings, as well as a larger body of data obtained from other species [44, 45], initiated considerable theoretical work in which the principles underlying the development of these patterns were explored. For a recent review see [45]. Many different models have been proposed during the past two decades. However, the different approaches have rarely been thoroughly compared with each other, nor have many of them been tested against the recent experimental data.

Hence, we have critically evaluated the most prominent and successful of the alternative modeling approaches. Such a study serves several purposes: Firstly, it may help to exclude certain approaches; secondly, it may reveal that seemingly different models are actually related or based on similar principles; thirdly, it may help to determine which quantities can be computed to allow model comparisons; and, finally, it may reveal which of these quantities are most useful for deciding between hypotheses.

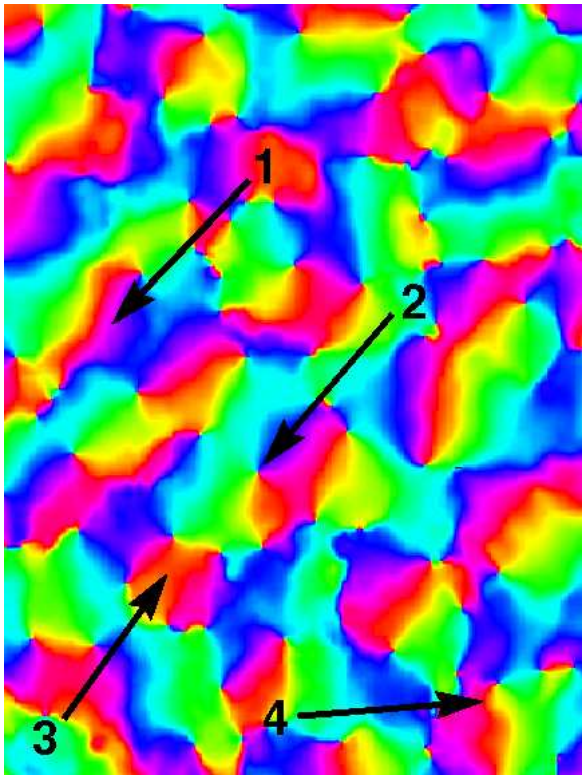

Figure 7: Lateral spatial pattern of orientation preference in the striate cortex of an adult macaque as revealed by optical imaging: The figure [35] shows a 4.1 mm × 3.0 mm surface region located near the border between cortical areas 17 and 18 and close to the midline. (Animal NM1 in [36]) Local average orientation preference is indicated by color such that the interval of 180° is mapped onto a color circle. Arrows indicate (1) linear zones, (2) singularities, (3) saddle points, and (4) fractures.

Our research is a first step in this direction. We extracted principles of organization from recent data obtained from monkey striate cortex (see Figure 7) and developed numerical tests to demonstrate these properties. We applied these tests to the predictions of a large number of models for the formation of orientation and ocular dominance maps. Although seemingly based on different assumptions, most models produced maps which qualitatively resemble the experimentally obtained maps. In order to sort through the conflicting models that were previously proposed, we extended and analyzed some of the prominent models and compared their predictions with the experimental data. The results of our comparison between model predictions and experimental data obtained from the upper layers of macaque striate cortex are summarized in [46]. Several models were found to predict patterns which are inconsistent with the data and, thus, are not sufficient models of macaque map structure or development, regardless of the plausibility of the proposed physiological mechanisms. As data becomes available from more species and under manipulated developmental conditions, the tests developed in the Resource will help compare model predictions with such data.

BRTP UNIT: T

TITLE: Molecular Modeling: The Program `namd`

KEYWORDS: molecular dynamics, spatial decomposition, parallel

AXIS I: 9

AXIS II: 42 84

INVEST1: Mark T. Nelson
DEGREE1: BS
DEPT1: CS
NONHOST1:

INVEST2: Attila Gursoy
DEGREE2: PhD
DEPT2: CS
NONHOST2:

INVEST3: Robert Brunner
DEGREE3: BS
DEPT3: EE
NONHOST3:

% BRTP $: 16

ABSTRACT: The program `namd` is a molecular dynamics program designed for simulations of large biological macro-molecular systems over long time scales. Specifically, `namd` exploits the computational power of distributed memory parallel computers and provides a modular design that allows the implementation of new algorithms. The program `namd` uses spatial decomposition coupled with a multithreaded, message driven design that provides a scalable, efficient parallel framework. One new algorithm that has been incorporated is the distributed parallel multipole tree algorithm [1] which allows full electrostatic force evaluation in $O(N)$ time. A novel use of `namd` is interactive molecular dynamics, where researchers can view and interact with a running simulation in real time. As part of the MDScope [2] software package, `namd` is connected via `MDComm` to the molecular graphics program `vmd` to provide such an interactive system. The computational capabilities of `namd` are currently being used to study systems such as the poliovirus coat and the estrogen receptor. Source code, documentation, and precompiled binaries are available via anonymous ftp from the site `ftp.ks.uiuc.edu` in the directory `/pub/mdscope/namd`.

BRTP UNIT: D

TITLE: Molecular Visualization: The Program `vmd`

KEYWORDS: molecular graphics, interactive visualization

AXIS I: 9

AXIS II: 42 70

INVEST1: William Humphrey
DEGREE1: MS
DEPT1: Physics
NONHOST1:

INVEST2: Andrew Dalke
DEGREE2: MS
DEPT2: Physics
NONHOST2:

INVEST3: Rick Kufrin
DEGREE3: BS
DEPT3: Psychology
NONHOST3: National Center for Supercomputing Applications

% BRTP $: 16

ABSTRACT: The program `vmd` is an interactive molecular visualization program currently under development by the Resource, intended for use as both a stand-alone molecular graphics system and as an interactive visual front-end for the program `namd` which is also under development by the Resource [2]. Using `vmd`, researchers can view biomolecular structures and visualize the results of molecular dynamics (MD) simulations with a variety of display and coloring options. Combined with the program `namd`, `vmd` works as the visual component of `MDScope`, an extensive problem-solving environment for MD studies in structural biology. `vmd` can be used to initiate a simulation of a biopolymer with `namd` on another computer, and can display the results of the simulation as they are calculated, as well as control the simulation parameters. `vmd` works with a variety of display and input devices, such as a large-screen stereo projection system coupled to a spatial tracking device which acts as a three-dimensional pointer. This program, together with documentation and complete C++ source code, is freely available for researchers from the anonymous ftp server `ftp.ks.uiuc.edu`, in the directory `/pub/mdscope/vmd`.

BRTP UNIT: C

TITLE: Molecular Dynamics Simulation of Membranes and Protein–membrane interactions

KEYWORDS: IAM, PC, C10, Phospholipase A_2, MD, drug–membrane interaction, protein–membrane interaction, interfacial activation

AXIS I: 6 9

AXIS II: 74f,h

INVEST1: Qing Sheng
DEGREE1: PhD
DEPT1: Physics
NONHOST1: Cornell University

INVEST2: Feng Zhou
DEGREE2: BS
DEPT2: Biology
NONHOST2:

INVEST3: Charles Pidgeon
DEGREE3: PhD
DEPT3: Medicinal Chemistry
NONHOST3: Purdue University

INVEST4: Cheng Yong Yang
DEGREE4: MS
DEPT4: Biochemistry
NONHOST4: Purdue University

% BRTP $: 6

ABSTRACT: Immobilized artificial membranes (IAMs) are model membranes which are used to predict solute partition in membranes and are used to purify membrane proteins. For the first time, a 250 ps molecular dynamics simulation of an IAM-PC surface was performed by the Resource in collaboration with Charles Pidgeon and Cheng Yong Yang at Purdue University using the resource cluster and the program X-PLOR. The program `vmd` was used for visualization and data analysis. The results were compared to previous MD simulations of membrane lipids and the IAM surface was found to be distinct from the surfaces in fluid membranes. The computer generated IAM surface used for the simulation contained 36 phosphatidylcholine (PC)

molecules and 2487 water molecules. In addition, seven straight chain alkanes were intercalated between the 36 PC molecules to simulate the experimental end capping performed during the synthesis of IAMs. The interfacial distributions of glycerol and phosphatidylcholine groups were virtually identical in both fluid and immobilized membranes. This indicated that the polar interfacial region of IAM was very similar to fluid membranes. Water molecules were strongly polarized at the IAM interfacial region. Water polarization decayed exponentially from the first hydration layer to the bulk water with a decay length of 13 Å. Water penetrated only to the ester group region during simulation. The diffusion of water near the membrane headgroups was found to be twice as fast in the plane of the membrane as in the direction that is normal to the membrane. The internal phosphate diffusion rate calculated from the dynamics was 1.7 ns^{-1} which is close to the NMR experimental value of 1.0 ns^{-1}. Collectively, the simulation results suggest the IAM polar head group region is similar to the interfacial region of fluid membranes but the hydrocarbon part of the IAM has unique physical-chemical properties. The simulation results explain, in part, why IAMs can be experimentally used to measure membrane partition coefficients for drugs and solutes.

Interaction between the enzyme human synovial phospholipase A_2 and a dilaurylphosphatidylethanolamine lipid monolayer has been studied by molecular dynamics simulations as a collaboration with Eli Lilly research laboratories. The modelling studies were carried out using the Resource cluster, the program PMD for simulation and `vmd` for visualization. Two enzyme–membrane complexes were investigated, a tightly bound protein–membrane complexes and a loosely bound protein–membrane complex. A simulation has also been carried out for the enzyme in aqueous solution. Phospholipase A_2 behaves as a robust molecule and no significant conformational differences were observed for all simulations. Hydrogen bonds and salt bridges formed between the protein and lipid molecules were found and effects of such interactions on lipid head group dynamics were analyzed. Solvation free energies of the lipid head groups were calculated for the lipid molecules in the enzyme–membrane complexes and indicate a desolvation for lipids interacting with protein hydrophobic residues for a tightly bound protein–membrane complex. The charge–charge interaction between the protein and negatively charged lipid head groups were investigated by assuming a partial deprotonation of the ethanolamine lipid head groups. The protein–membrane microinterface was found to have a positive but inhomogeneous potential and negatively charged lipid head groups were favored. The calculations support the model proposed by observations that desolvation of lipids plays an important role in the activation of phospholipase A_2 on membrane surface.

BRTP UNIT: C

TITLE: Molecular Dynamics Study of the Bacteriorhodopsin Photocycle

KEYWORDS: bacteriorhodopsin, membrane protein, bR, retinal, molecular dynamics, photocycle, water

AXIS I: 2 6 7a

AXIS II: 74h

INVEST1: William Humphrey
DEGREE1: MS
DEPT1: Physics
NONHOST1:

INVEST2: Dong Xu
DEGREE2: MS
DEPT2: Physics
NONHOST2:

INVEST3: Mordechai Sheves
DEGREE3: PhD
DEPT3: Organic Chemistry
NONHOST3: Weizmann Institute, Israel

% BRTP $: 16

ABSTRACT: Bacteriorhodopsin (bR), a retinal protein in the purple membrane of *Halobacterium halobium*, is known to function as a light-driven proton pump, which generates an electrochemical potential gradient across the cell membrane. This gradient is then utilized for ATP synthesis.

The bR photocycle, including the J_{625}, K_{590}, L_{550} and M_{412} intermediates, and the role of water molecules within the protein interior, are studied by means of molecular dynamics simulations based on a refined structure of bR_{568} [25]. The simulations were carried out with X-PLOR on Silicon Graphics and Hewlett-Packard workstations at the Resource. The following questions were addressed: How do the binding site and the excited state potential surface control retinal's photoisomerization? How is the initial photoreaction affected by a lowering of temperature? What are the driving forces for the formation and the decay of the M_{412} intermediate, and how do retinal, the protein and internal water molecules cooperate to realize the proton switch function?

To model the quantum yield of the $bR_{568} \rightarrow J_{625}$ transition, i.e., the dependence of the dynamics on initial conditions, 50 separate isomerization trials are completed for each potential surface, at both 300 K and 77 K [47]. The trials are distinguished by different initial, random velocity distributions. From these trials, beside all-*trans* retinal, three different photoproducts emerge as candidates for the K_{590} intermediate: (1) 13-*cis* retinal, with the Schiff base proton oriented toward Asp-96; (2) 13-*cis* retinal, highly twisted around the C_6-C_7 bond, with the Schiff base proton oriented perpendicular to the membrane normal; (3) 13,14-*dicis* retinal with the Schiff base proton oriented towards the extracellular side. Two candidates for the K_{590} intermediate, case (2) and case (3) above, were subjected to simulated annealing to determine corresponding L_{550} and M_{412} structures. We suggest that photoproduct (2) above most likely represents the true K_{590} intermediate. Water molecules near the Schiff base binding site are found to play a crucial role in stabilizing the K_{590} state and in establishing a pathway for proton transfer to Asp-85.

The M_{412} intermediate is initiated through proton transfer to Asp-85 based on the corresponding L_{550} structures. Our simulations reveal that the M_{412} intermediate actually constitutes a series of conformational changes involving (a) a motion of retinal, (b) protein conformational changes, and (c) diffusion and reconfiguration of water in the space between the retinal Schiff base nitrogen and Asp-96 change. Here, (a) turns the retinal Schiff base nitrogen from an early orientation towards Asp-85 to a late orientation towards Asp-96, (b) disconnects the hydrogen bonding network between retinal and amino acid side groups from Asp-85 and tilts helix F of bR, enlarging bR's cytoplasmic channel, and (c) adds two water molecules to three water molecules existing in the cytoplasmic channel at the bR_{568} stage and forms a proton conduction pathway. The observed conformational change (b) of the protein involves a 60° bent of the cytoplasmic side of helix F and is induced through a break of hydrogen bonding between Tyr-185 and a water side group complex in the counterion region.

BRTP UNIT: T

TITLE: Combined Quantum Chemistry and Molecular Dynamics Study of Retinal Spectral Properties and the Dark Adaptation Process in Bacteriorhodopsin

KEYWORDS: ab initio, retinal, spectra, dark adaptation

AXIS I: 2 6 7a

AXIS II: 74h

INVEST1: Ilya Logunov
DEGREE1: MS
DEPT1: Chemistry
NONHOST1:

INVEST2: Charles Martin
DEGREE2: PhD
DEPT2: Chemical Physics
NONHOST2:

% BRTP $: 10

ABSTRACT: The determination of a low resolution structure of bacteriorhodopsin (bR) [48] and its refinement by means of molecular dynamics simulations [49, 50, 25] now allows a rigorous study of the electronic structure, ground state (S0) and excited state (S1) potential surfaces of retinal in the bR binding site.

We have employed a combination of molecular dynamics and quantum chemistry techniques to study the electronic excitation and conformational potential surface of retinal in the bR binding site. Calculations have been performed for both the ground state (S0) and the first excited singlet (S1) state. The CASSCF(6,9)/6-31G level of *ab initio* calculations (within Gaussian92) has been used for the treatment of both the ground and excited states of retinal. Charges of all atoms in the protein are represented by spherical Gaussians and explicitly included in the electronic Hamiltonian of retinal.

Spectral properties have been analyzed for the native bR pigment as well as for its D85N mutant. The technique employed was found to be adequate for treating the electronic excitation of the chromophore *in situ*. However, absolute quantitative agreement with experiment has only been achieved for the value of the relative shift of the absorption maximum, and not for the absolute parameters of the absorption line shape. The correlation function for the energy of the electronic S0 $\rightarrow$ S1

transition of *in situ* retinal has been analyzed on various time scales. It is concluded that the absorption spectrum of *in situ* retinal is strongly affected by a number of factors, such as electrostatic interactions, dihedral torsions, and hydrogen bonding to the Schiff base NH group.

The dark adaptation process in bR involves a reversible thermally activated transformation of retinal from an all-trans to a 13-*cis*,15-*syn* configuration. The potential surface governing the thermal isomerization of retinal around two (13-14, 15-N) double bonds has been characterized. The placement of retinal in the bR active site considerably reduces its isomerization barrier. Thermal fluctuations of the protein interior lead to a further reduction of the effective activation energy. Our simulations support the notion that the isomerization process is catalyzed by the protonation of an aspartic acid (Asp85) side group of bacteriorhodopsin.

BRTP UNIT: C

TITLE: Prediction of the Structure of an Integral Membrane Protein–the Light-Harvesting Complex II of *Rhodospirillum molischianum*

KEYWORDS: Light-harvesting complex, purple bacteria, protein folding, protein structure, membrane protein

AXIS I: 6 7a

AXIS II: 52 74h

INVEST1: Xiche Hu
DEGREE1: PhD
DEPT1: Chemistry
NONHOST1:

INVEST2: Dong Xu
DEGREE2: MS
DEPT2: Physics
NONHOST2:

INVEST3: Kenneth Hamer
DEGREE3: MS
DEPT3: Physics
NONHOST3:

INVEST4: Hartmut Michel
DEGREE4: PhD
DEPT4: Biochemistry
NONHOST4: Max-Planck-institut für Biochemie,Frankfurt, Germany

INVEST5: Juergen Koeppke
DEGREE5: PhD
DEPT5: Biochemistry
NONHOST5: Max-Planck-institut für Biochemie,Frankfurt, Germany

% BRTP $: 8

ABSTRACT: We attempted to predict the structure of the light-harvesting complex II (LH-II) of *Rhodospirillum molischianum* through computer simulations, in collaboration with Hartmut Michel at the Max Planck Institute, Frankfurt, Germany. The photosynthetic apparatus of purple bacteria consist of two types of protein-pigment complexes: the reaction centers and the light-harvesting complexes. The main function of the light-harvesting complexes is to collect and transfer light energy to the reaction centers where primary charge separation takes place. In most purple bacteria, the photosynthetic membranes contain two types of light-harvesting complexes [51]: light harvesting complex I (LH-I) and light harvesting complexes II (LH-II) [52].

Michel's group has crystallized the LH-II complex of *Rhodospirillum molischianum* and collected X-ray diffraction data with 2.4 Å resolution [53]. However, the conventional approach to solve the phase problem, i.e., isomorphous replacement, has been unsuccessful due to the technical difficulty in making heavy metal derivatives of the complex. An alternative solution is to phase the structure by using a homologous structure in a procedure called molecular replacement [54, 55]. In the molecular replacement method, normal practice is to employ a probe structure of a protein X to solve the unknown structure of protein Y when X and Y have a high degree of homology. In the present case, there exists no highly homologous structure to LH-II, and the probe structure is obtained through molecular modeling.

The LH-II of *Rhodospirillum molischianum* is composed of 16 membrane spanning polypeptides which aggregate and bind 24 bacteriochlorophyll a's and 12 lycopenes. Hydropathy analysis was performed to identify the putative transmembrane segments, which were then independently verified by multiple sequence alignment propensity analyses and homology modeling. A consensus assignment for secondary structure was derived from combination of all the prediction methods used. Transmembrane helices were built by comparative modeling. The resulting tertiary structures were then aggregated into a quaternary structure through molecular dynamics simulations followed by energy minimization under constraints provided by site directed mutagenesis and FT Resonance Raman spectra, as well as conservation of residues. The structure of LH–II so determined is an octomer of $\alpha\beta$ heterodimers forming a ring with a diameter of 70 Å. All simulations were carried out with the HP workstation cluster at the Resource using X-PLOR and `vmd`. Details of this work have been recently submitted for publication [56].

BRTP UNIT: C

TITLE: Molecular Dynamics Study of Protein–DNA Interactions

KEYWORDS: DNA, protein–DNA interaction, transcription regulation, hormone, receptor, molecular dynamics

AXIS I: 9

AXIS II: 74e,g,h

INVEST1: Alexander Balaeff
DEGREE1: MS
DEPT1: Biophysics
NONHOST1:

INVEST2: Thomas C. Bishop
DEGREE2: MS
DEPT2: Chemistry
NONHOST2:

INVEST3: Dorina Kosztin
DEGREE3: BS
DEPT3: Physics
NONHOST3:

INVEST4: Jim Schnitzer
DEGREE4: MS
DEPT4: Chemistry
NONHOST4:

INVEST5: Mair Churchill
DEGREE5: PhD
DEPT5: Biophysics
NONHOST5:

% BRTP $: 6

ABSTRACT: The process of gene transcription is regulated by a host of regulatory proteins called transcription factors. Transcription factors bind directly to DNA to either promote or inhibit transcription resulting in increased or decreased expression. We are studying the details of these protein–DNA interactions and the effects which complex formation has on the conformation of the interacting molecules for two families of transcription factors, the nuclear hormone receptors and the high mobility groups.

We began the study of nuclear hormone receptors with molecular dynamics simulations of the complex formed by a DNA segment and a dimer of glucocorticoid receptor – DNA binding domains (GR-DBD), employing an available X-ray structure [57]. Our analysis focused on deformations of the DNA that were induced by the binding of GR [58] and on a comparison of complexes which contained different DNA sequences [59]. The deformations observed involve a 35° bend of the DNA, an unwinding and a displacement of the helical axis. These deformations are consistent with a mechanism for transcriptional regulation that involves a change of nucleosome packing upon GR binding. Biologically significant protein–protein and protein–DNA interactions, both direct and water mediated, developed in our simulations due to the deformations of the DNA. These interactions include direct interactions between the DNA and glycine 458 and serine 459 of the human GR. These amino acids are crucial in differentiating a GR from other members of the nuclear hormone receptor family.

The study of nuclear hormone receptors is currently being extended to include simulations of a dimer of estrogen receptor-DBD's (ER-DBD) complexed with DNA based on the X-ray structure [60]. These simulations are being prepared and tested on the HP cluster administered by the Resource, while final production runs will be conducted on supercomputers. A typical simulation consists of approximately 40,000 atoms and will require a minimum of 100 ps of simulations time. We are using the molecular dynamics software package `MDScope` for these simulations in order to develop and to test it for biological applications and on various computational platforms.

The high mobility group (HMG) proteins include both sequence specific and sequence non-specific DNA binding proteins supposedly involved in chromatin packing (see [61] for review). Both types of HMG share a common DNA binding domain called the HMG box. This domain was resolved recently by NMR [62, 63] and revealed a novel DNA binding motif. A collaborative effort with Dr. M. Churchill is devoted to the prediction of the structure of the complex between DNA and HMG-D chromosomal protein from *Drosophila melanogaster*. HMG-D is of the sequence non-specific binding type. For this purpose protocols using various molecular dy-

namics methods for predicting the structure of the protein–DNA complex based on the available experimental data are currently being developed for use with `namd`.

BRTP UNIT: C

TITLE: Modeling the Morphogenesis of the Lateral Geniculate Nucleus

KEYWORDS: macaque monkey, development, pattern formation, thalamus

AXIS I: 1d,21,25b

AXIS II: 41,60,77

INVEST1: Svilen Tzonev
DEGREE1: MS
DEPT1: Physics
NONHOST1:

INVEST2: Joseph Malpeli
DEGREE2: PhD
DEPT2: Psychology
NONHOST2:

% BRTP $: 12

ABSTRACT: The macaque lateral geniculate nucleus (LGN) exhibits an intricate lamination pattern: depending on the visual eccentricity, it has regions with 6, 4, and 2 distinct layers. The transition from 6 to 4 layers always coincides with the position of small cell-free gaps corresponding to the blind spot in the retina. We have developed a 3-D model in which local cell interactions cause a wave of development of neuronal receptive fields to propagate through the nucleus and establish distinct lamination patterns. The initial (6-layered) pattern is maintained and propagated along the LGN by strict retinotopy, cell interactions promoting clustering of cells with similar functionality, as well as external gradients. The initial pattern gradually becomes unstable and perturbations due to the blind spot gaps induce a sharp transition to a more stable 4-layered pattern. Critical factors for the final global lamination pattern are: initial (foveal) pattern, cell interaction distances, size and location of the gaps and the shape of the developmental wavefront.

The human LGN exhibits a similar global organization with regions with 2, 4 and 6 layers. The relation between the position of the blind spot gaps and the transition, however, is not as sharply defined: the transition occurs at a varying location with higher visual eccentricity than the gaps. We explore differences in the parameters of the human and macaque LGN models in order to understand the nature of the observed pattern transitions. It appears that the macaque transition is induced by the gaps, while the human transition is more spontaneous. At the eccentricity of

the gaps, the relative stabilities of the two laminar patterns do not favor a sharp transition; such transitions occur spontaneously after the gaps, thus the variance in its position.

BRTP UNIT: T

TITLE: Models of Orientation and Ocular Dominance Columns in the Visual Cortex: A Critical Comparison

KEYWORDS: macaque monkey, brain maps, visual cortex, orientation selectivity, ocular dominance

AXIS I: 25b 21

AXIS II: 77 41 60 63

INVEST1: Edgar Erwin

DEGREE1: PhD

DEPT1: Chemical Physics

NONHOST1:

% BRTP $: 4

ABSTRACT: Orientation selectivity and ocular dominance maps in the mammalian primary visual cortex are among the most thoroughly investigated patterns in the cerebral cortex. Many competing models of the formation of these maps have been proposed. Some models focus on development of receptive fields while others focus on the structure of cortical maps, i.e. the arrangement of receptive field properties across the cortex. In each scheme, different means are used to evaluate successful reproduction of the experimental data. Often, visual comparison is used as the main tool.

We critically evaluate and compare, with the available data from macaque striate cortex, more than ten of the most prominent models of map formation and structure. Comparisons are based on properties of the predicted or measured cortical map patterns. We introduce several new measures for comparing experimental and model map data which reveal important differences between models. We expect that the use of these measures will improve current models by helping determine parameters to match model maps to experimental data now becoming available from a variety of species.

Our study reveals that despite apparent differences, many models are based on similar principles and consequently make similar predictions. Several models produce orientation map patterns which are inconsistent with the experimental data from macaques, regardless of the plausibility of the models' suggested physiological implementations. No models have yet fully accounted for both the local and the global relationships between orientation and ocular dominance map patterns.

BRTP UNIT: T

TITLE: Biologically Plausible Neural Architectures for Visuo-motor Control

KEYWORDS: motor control,information processing,movement,robotics

AXIS I: 9 21

AXIS II: 41 77 84

INVEST1: K. R. Wallace
DEGREE1: D.Phil.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: Michael Zeller
DEGREE2: Dipl. Physics
DEPT2: Physics
NONHOST2: University of Frankfurt

% BRTP $: 6

ABSTRACT: In previous investigations [64], we have addressed the issue of how anatomically and, apparently, functionally distinct motor areas of the primate motor system can jointly program goal-directed movement. This has been achieved through the development of a computational model of some of the neural systems responsible for motor control. The resulting model exhibits the capability of learning new movements in a manner similar to that observed in primates during the acquisition of motor skills.

The neural architecture developed for this work has now being applied to the problem of controlling movement of a robotic manipulator in three-dimensional space. Such control raises both theoretical and practical issues. From the theoretical perspective it is desirable that the information processing stages developed be consistent with the known neurobiology. From a practical standpoint one of the primary goals of the present work is to develop more robust and biologically plausible computational techniques, than have been employed hitherto [65], to extract information from the visual field necessary to permit accurate control of movement. This work is being undertaken in collaboration with members of the Artificial Intelligence Group located in the Beckman Institute. Initial investigations of this problem demonstrated the limitations of the original computational resources employed for

this purpose. Furthermore it was evident that the increasing computational complexity of the neural architectures being developed would seriously aggravate this problem.

Consequently a complete upgrade of all hardware associated with the control of the manipulator has been undertaken. This has included the acquisition of a vision processing system capable of processing images of the visual field in real-time. In addition a HP workstation with a direct connection to the HP workstation-cluster operated by the Resource is now employed as the platform from which control of the hardware dedicated to the control of the robot is effected. Such an arrangement presents the opportunity to harness the additional computational resources provided by the cluster when necessary.

Closely coupled with this effort, further work continues to be undertaken into elaborating the mechanisms underlying the operation of the neuronal networks of the primate motor system implicated in visuo-motor control.

	TECH RES & DEVEL (T)	COLLAB RES & SERVICE (C)	DISSEM & TRAINING (D)	TOTALS
NUMBER OF PUBLICATIONS	15	10	1	26
NUMBER OF SUBPROJECTS	4	5	1	10
NUMBER OF INVESTIGATORS	8	19	3	30[1]
PERCENT OF BRTP FUNDS ALLOCATED	36%	48%	16%	100%
SERVICE FEES COLLECTED	0	0	0	0
OTHER FUNDS ($)	640,000	123,000	–	763,000

[1]W. Humphrey is counted twice: once in the BRTP unit "C", and once in the BRTP unit "D". I. Logunuv is also counted twice: once in the BRTP unit "T", and once in the BRTP unit "C".

State or Country	Number of Investigators
IL	22
IN	2
Israel	1
Germany	3

BRTP Unit T

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Brunner, Robert	University of Illinois (Kale, Laxmikant)	FED	NIH
Erwin, Edgar	University of Illinois (Schulten, Klaus)	FED	NIH
Gursoy, Attila	University of Illinois (Kale, Laxmikant)	FED	NSF
Logunov, Ilya	University of Illinois (Schulten, Klaus)	FED OTH	NIH
Martin, Charles	University of Illinois (Schulten, Klaus)	FED	NIH
Nelson, Mark	University of Illinois (Skeel, Robert)	FED	NIH
Wallace, K. R	University of Illinois (Schulten, Klaus)	FED	NIH
Zeller, Michael.	University of Frankfurt, Germany (Schulten, Klaus)	OTH	

BRTP Unit C

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Balaeff, Alexander	University of Illinois (Schulten, Klaus)	OTH	
Bishop, Thomas	University of Illinois (Schulten, Klaus)	FED	NSF, NIH
Churchill, Mair	University of Illinois (Churchill, Mair)	OTH	
Hamer, Kenneth	University of Illinois (Schulten, Klaus)	OTH	
Hu, Xiche	University of Illinois (Schulten, Klaus)	OTH	
Humphrey, William	University of Illinois (Schulten, Klaus)	FED	NSF, NIH
Koeppke, Juergen	Max–Planck–Institute for Biophysics, Germany (Michel, Hartmut)	OTH	
Kosztin, Dorina	University of Illinois (Schulten, Klaus)	OTH	
Logunov, Ilya	University of Illinois (Schulten, Klaus)	FED OTH	NIH
Malpelli, Joseph	University of Illinois (Malpelli, Joseph)	FED	NIH

BRTP Unit C (cont.)

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Michel, Hartmut	Max–Planck–Institute for Biophysics, Germany (Michel, Hartmut)	OTH	
Pidgeon, Charles	Purdue University (Pidgeon, Charles)	OTH	
Schnitzer, Jim	University of Illinois (Schulten, Klaus)	OTH	
Sheng, Qing	University of Illinois (Schulten, Klaus)	OTH	
Sheves, Mordechai	The Weizmann Institute, Israel (Sheves, Mordechai)	OTH	
Tzonev, Svilen	University of Illinois (Schulten, Klaus)	FED	NIH
Xu, Dong	University of Illinois (Schulten, Klaus)	FED	NIH
Yang, Cheng Yong	Purdue University (Pidgeon, Charles)	OTH	
Zhou, Feng	University of Illinois (Schulten, Klaus)	FED	NIH

BRTP Unit D

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Dalke, Andrew	University of Illinois (Schulten, Klaus)	OTH	
Humphrey, William	University of Illinois (Schulten, Klaus)	FED	NSF, NIH
Kufrin, Rick	University of Illinois (NCSA)	FED	NSF

BRTP unit: (T)

NUMBER PUBLISHED –
Books: 0 Papers: 4 Abstracts: 0

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

PUBLISHED:

* E. Erwin, K. Obermayer, and K. Schulten: "Models of Orientation and Ocular Dominance Columns in the Visual Cortex: A Critical Comparison", *Neural Comp.*, **7**, 425–468 (1995).

* T. Hesselroth, K. Sarkar, P. P. van der Smagt, and K. Schulten: "Neural Network Control of a Pneumatic Robot Arm", *IEEE Trans. on Systems, Man and Cybernetics*, **24**(1), 28–37 (1994).

* L. Kalé: "Suggesting HPCC Agendas", in U. Vishkin, Ed., "Application Orientated and Computer Science Centered HPCC Research". ACM Press, 1994.

* I. Logunov, W. Humphrey, K. Schulten, and M. Sheves: "Molecular Dynamics Study of the 13-*cis* Form (bR_{548}) of Bacteriorhodopsin and Its Photocycle", *Biophys. J.*, **68**, 1270–1282 (1995).

IN PRESS OR SUBMITTED:

* D. Barsky, B. Pütz, and K. Schulten: "Exploiting Bi-Exponential Relaxation to Detect Capillaries in MRI", *Magn. Reson. Med.*, Submitted. [Beckman Institute Technical Report TB-91-23].

* T. Bishop, H. Heller, and K. Schulten: "Molecular Dynamics on Parallel Computers: Applications for Theoretical Biophysics", in R. K. Kalia and P. Vashishta, Eds., "Toward Teraflop Computing and New Grand Challenge Applications". Nova Science Publishers, Inc., New York, 1995, In Press.

* E. Erwin, K. Obermayer, and K. Schulten: "A Critical Comparison of Models for Orientation and Ocular Dominance Columns in the Striate Cortex", in T. G., T. D., and A. J., Eds., "Advances in Neural Information Processing Systems 7". Morgan Kaufmann Publishers, 1995, In press.

* C. Kurrer and K. Schulten: "Noise-Induced Neuronal Oscillations", *Phys. Rev. E*, In Press. [Beckman Institute Technical Report TB-93-16].

* K.-R. Müller, M. Finke, N. Murata, K. Schulten, and S. Amari: "Large Scale Simulations for Learning Curves", in "Proceedings of the Workshop on the Theory of Neural Networks: The Statistical Mechanics Perspective". World scientific, POSTECH, Pohang, Korea, 1995, In press.

* M. Nelson, W. Humphrey, A. Gursoy, A. Dalke, L. Kalé, R. Skeel, K. Schulten, and R. Kufrin: "MDScope – A Visual Computing Environment for Structural Biology", *Comput. Phys. Commun.*, In press. [Beckman Institute Technical Report TB-94-18].

* J. Phillips and K. Schulten: "Modeling AFM Tip Dynamics Through Diffusion in Time-Periodic Potentials", in H. Gaub, Ed., "NATO Advanced Research Workshop on Atomic Force Microscopy", in *NATO ASI Series B*. Plenum Press, New York, 1995, In press. [Beckman Institute Technical Report TB-95-03].

* K. Sarkar and K. Schulten: "Topology Representing Network in Robotics", in J. L. van Hemmen, E. Domany, and K. Schulten, Eds., "Physics of Neural Networks, Volume 3". Springer–Verlag, New York, 1995, In press. [Beckman Institute Technical Report TB-93-15].

* K. R. Wallace and K. Schulten: "A Model of Cortical Processing During Motor Learning", *Biol. Cybernetics*, Submitted. [Beckman Institute Technical Report TB-94-11].

* D. Xu and K. Schulten: "Velocity Reassignment Echoes in Proteins", *J. Chem. Phys.*, In press. [Beckman Institute Technical Report TB-95-01].

* D. Xu, K. Schulten, O. M. Becker, and M. Karplus: "Temperature Quench Echoes in Proteins", *J. Chem. Phys.*, In press. [Beckman Institute Technical Report TB-95-02].

BRTP unit: (C)

NUMBER PUBLISHED –
Books: 0 Papers: 4 Abstracts: 0

NUMBER IN PRESS OR SUBMITTED–
Books: 0 Papers: 6 Abstracts: 0

PUBLISHED:

* T. Bishop and K. Schulten: "Molecular Dynamics Study of a Sequence Specific Protein–DNA Interaction", in G. Wipff, Ed., "Computational Approaches in Supramolecular Chemistry", pages 419–439. Kluwer Academic Publishers, Boston, 1994.

* J. A. Board, Jr., L. V. Kalé, K. Schulten, R. D. Skeel, and T. Schlick: "Modeling Biomolecules: Larger Scales, Longer Durations", *IEEE Trans. on Computat. Sci. and Eng.*, **winter issue**, 19–30 (1994).

* B. Pütz, D. Barsky, and K. Schulten: "Mechanisms of Liposomal Contrast Agents in Magnetic Resonance Imaging.", *J. Liposome Res.*, **4**(2), 771–808 (1994).

* F. Zhou and K. Schulten: "Molecular Dynamics Study of a Membrane–Water Interface", *J. Phys. Chem.*, **99**, 2194–2208 (1995).

IN PRESS OR SUBMITTED:

* T. Bishop and K. Schulten: "Molecular Dynamics Study of Glucocorticoid Receptor–DNA Binding", *Proteins*, Submitted. [Beckman Institute Technical Report TB-94-17].

* J. M. Canfield, R. L. Belford, P. G. Debrunner, and K. Schulten: "A Perturbation Treatment of Oscillating Magnetic Fields in the Radical Pair Mechanism Using the Liouville Equation", *Chem. Phys.*, **195** (1995), In press.

* X. Hu, D. Xu, K. Hamer, K. Schulten, J. Koepke, and H. Michel: "Predicting the Structure of the Light-Harvesting Complex II of *Rhodospirillum molischianum*", *Protein Science*, Submitted.

* W. Humphrey, D. Xu, K. Schulten, and M. Sheves: "Molecular Dynamics Study of the Early Intermediates in the Bacteriorhodopsin Photocycle", *Biophys. J.*, Submitted. [Beckman Institute Technical Report TB-95-05].

* Q. Sheng, K. Schulten, and C. Pidgeon: "A Molecular Dynamics Simulation of Immobilized Artificial Membranes", *J. Phys. Chem.*, Submitted. [Beckman Institute Technical Report TB-95-04].

* S. Tzonev, J. Malpeli, and K. Schulten: "Morphogenesis of the Lateral Geniculate Nucleus: How Singularities Affect Global Structure", in G. Tesauro, D. Touretzky, and J. Alspector, Eds., "Advances in Neural Information Processing Systems 7". Morgan Kaufmann Publishers, 1995, In press. [Beckman Institute Technical Report TB-94-13].

BRTP unit: (D)

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

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

PUBLISHED:

IN PRESS OR SUBMITTED:

* I. Kosztin, B. Faber, and K. Schulten: "Introduction to the Diffusion Monte Carlo Method", *Am. J. of Phys.*, Submitted. [Beckman Institute Technical Report TB-95-06].

Advisory committee

The next Resource Advisory Committee will meet on November 13, 1995 to review the success of past projects, the implementation of previous recommendations and to provide fresh advice on new research, technological directions, collaborations, and community needs.

The following colleagues will participate:

Bernie Alder, UC Berkeley, Physics (Computational Science)
Peter Arzberger, San Diego, SC
William Gear, NEC Research Inst. Inc, Princeton
Karl Hess, UIUC, Electrical Engineering (Computational Science)
Barry Honig, Columbia, Biochemistry (Computational Structural Biology)
Christoph von der Malsburg, USC, Neurobiology, and Ruhr-Universitt Bochum, Bochum, Germany
Attila Szabo, NIH

Training and Dissemination

The Resource has expanded its dissemination and training activities in the past year.

- In addition to publications and invited lectures, we continue to run a seminar series (see list of speakers and titles in the next section) and print a series of Beckman Institute Technical Reports. Resource members discuss their ongoing projects during weekly group meetings.

- The Resource maintains its use of several NCSA publications for distributing announcements and scientific results relating to developments in high–performance computing; these include Access (a general information newsletter), Datalink (a technical newsletter), and RealTime (a quarterly video journal).

- The Resource maintains a small yet well stocked library. There are 17 periodicals subscriptions to leading scientific, technology, and software development journals which include titles such as: *Current Opinion in Structural Biology, Nature, Mathematica Journal, Nature: Structural Biology, Science, and Issues in Science and Technology.* During the past year over 100 newly published books were purchased in areas such as Quantum Mechanics, Human Genetics, Mathematics, Biocomputing, Protein Folding, Protein Structure, Parallel Programming, Nonlinear Dynamics and Chaos, System Administration, and Neurobiology.

- The 3D projection facility has been extensively used for scientific, dissemination and training purposes, and for meeting community interest. The facility is regularly included on UIUC tours by federal and state officials, and is operated by the Resource personnel with demonstrations being made almost every day of the week. Visitors to the facility in the past year included: Illinois Senator Rauschenburger, Hartmut Michel (Max–Planck–Institut, Frankfurt), Pierre de Gennes (Ecole Normale Superieur, France), Stephen White (University of California, Irvine), Phillip Sharp (MIT), Stanley Ikenberry (current UIUC President), James Stukel (future UIUC president), Michael Klein (University of Pennsylvania), Stuart Schreiber (Harvard), Joseph Haggin (Senior Editor, *Chemical & Engineering News*), and Illinois High School Teachers Conference participants.

- The HP workstation cluster is being used by on–campus groups as well as outside users such as the Brunger Group at Yale, Board's group at Duke, Pidgeon's group at Purdue, and the Michel group at the Max–Planck–Institut for Biophysics Frankfurt.

- Documentation, source code and executable binaries for the program `vmd` are available from the ftp site `ftp.ks.uiuc.edu`, directory `/pub/mdscope/vmd`.

Documentation, source code and executable binaries for the program `namd` are available from the ftp site `ftp.ks.uiuc.edu`, directory `/pub/mdscope/namd`.

Documentation, source code and executable binaries for the program `MDComm` will be available soon from the ftp site `ftp.ks.uiuc.edu`, directory `/pub/mdscope/mdcomm`. Additionally, systematic retrieval records for all software will be available in the near future.

- Our HTTP server is regularly maintained to give all users of the Internet access to publications, images, and routine activities of the Resource. The average number of accesses per month is about 4,500. The address for our home page is `http://www.ks.uiuc.edu:1250/`.

- As part of the GCAG collaborative efforts with researchers from Yale (Axel Brunger), NYU (Tamar Schlick), and Duke (John Board), Resource members were instrumental in organizing and participating in a meeting at Yale in November of 1994. As before, the meeting provided an appropriate setting for the successful exchange of information and ideas between the four research groups.

- The Resource organized a 5–day workshop by Jan Hermans (UNC) and Ken Flurchick (NCSC) on January 23–27, 1995. The workshop entitled "Molecular Dynamics Simulations: Principles and Practice", reviewed the theory and practice of molecular dynamics simulations in a series of 9 lectures and 9 laboratory sessions. The lectures covered general principles and applications to problems of macromolecular structure and to kinetics of macromolecular processes. Applications to problems of thermodynamics of conformation change and molecular interactions received special emphasis. The workshop was successful in both fostering a meaningful dialogue between experimentalists and theorists, and in presenting methodological tools that are useful for the two groups. Participation was limited to UIUC scientists and consisted of a total of 22 senior graduate students, post doctoral associates and faculty members from departments such as Physics, Chemistry, Computer Science, Biophysics. The number of participants was determined by the instructors based on available facilities.

- In July of 1994, fifteen graduate students of the resource, including six new students attended the meeting on Protein Structure and Dynamics hosted by the Institute for Applied Mathematics at the University of Minnesota. The Resource participated in the coordination of the meeting which exposed the students to cutting-edge research in the field, and provided opportunity to interact with molecular biologists and mathematicians working on protein sequencing, protein folding, molecular dynamics, and the various mathematical, statistical, and computational aspects involved.

- In the summer of 1994 the Resource held a summer school for both incoming graduate students and group members. The program included a course on "Modelling Stochastic Behavior of Biopolymers" taught by Klaus Schulten, technical and scientific tutorials on a wide range of subjects pertinent to the group's research, and presentations by the new graduate students of their summer research projects.

- Plans for next year include: starting the publication of a newsletter; publishing an internal annual report early next fall; organizing a workshop for the Resource members focusing on the art of presentation and scientific writing; holding an Open House in the fall; investing in extensive dissemination efforts of `MDScope` and holding a training workshop to introduce the program to our collaborators and other interested scientists; hosting an X–PLOR workshop in the Summer of 96.

Outside Lectures

The PI presented the following invited lectures:

- May 30, 1994, NATO Advanced Research Workshop on "Organized Molecular Systems and Raster Electron Microscopy," Schloss Ringberg, Tegernsee, Germany; Lecture: *Molecular Dynamics Simulation of the Structure and Electrostatics of the Lipid–Water Interface*

- June 4, 1994, Protein Engineering and Design: Pfizer–Beckman Institute Symposium; Lecture: *Refinement of the Structure of Bacteriorhodopsin and its Photocycle Intermediates: Unravelling the Mechanism of a Proton Pump*

- June 8, 1994, Ceramics Engineering research group, University of Illinois, Urbana, IL; Lecture: *An Overview of Computational Biophysics*

- June 16, 1994, ZiF Conference "Prerational Intelligence in Robotics: From Sensorimotor Intellience to Collective Behavior", Bielefeld, Germany; Lecture: *Physics of Vision and of Visual Information Processing*

- July 8, 1994, Gordon Conference on Computational Chemistry, New Hampton School, NH; Lecture: *Simulations of Supramolecular Structures in Biology*

- July 22, 1994, Institute for Mathematics and its Applications - Summer Program: Structural Biology, Minneapolis, MN; Lecture: *Echoes, Bends, and Twists in Proteins and DNA* and Tutorial

- July 28, 1994, Futures in Science and Engineering, pre–college program for top high school sophomores and juniors, Urbana, IL; Lecture: *An Overview of Biophysics*

- August 21–22, 1994, American Chemical Society meeting, Washington, DC; Lectures: *Long Range Force Molecular Dynamics Study on Electrostatic and Other Properties of a Membrane–Water Interface* and *Molecular Dynamics Simulations of a Workstation Cluster Connected Through An ATM Switch*

- October 4–6, 1994, U.S.–Israel Workshop on HPCC and GII, Mamat Rachael, Israel; Lecture: *Computational Developments Needed for Progress in Biomedical Research*

- September 29–October 1, 1994, 18th Gwatt Workshop Computational Physics and Chemistry, Gwatt, Switzerland; Lecture: *Simulation of Supramolecular Structures in Biology*

- November 1, 1994, Department of Chemistry, MIT, Cambridge, MA; Lecture: *Molecular Dynamics Investigation of the Proton Pump Cycle of Bacteriohodopsin*

- November 3, 1994, The Rowland Institute for Science, Cambridge, MA; Lecture: *Molecular Dynamics Studies of Biomolecular Aggregates*

- November 15–20, 1994, University of California, Institute for Theoretical Physics, Santa Barbara, CA; Lecture (Colloquium): *Breaking the Riddle of a Biomolecular Device: Molecular Dynamics Study of the Light–Driven Proton Pump Bacteriorhodopsin*; Special Seminar: *Biomolecular Complexes and Aggregates, the New Frontier in Molecular Biophysics*

- February 3, 1995, Eli Lilly, Indianapolis, IN; Lecture: *Modeling Supra Molecular Structures: Protein–Protein, Protein–DNA, and Protein–Membrane Complexes*

- February 9, 1994, IBM, T.J. Watson Research Center, New York, NY Lecture: *Parallel Molecular Dynamics Simulations on Workstation Clusters*

- March 2, 1995, North Carolina Supercomputing Center, Research Triangle Park, NC Lecture: *Visual Computing for Structural Biology: Computational Technology and Applications to Membranes, Membrane Proteins as well as Protein–DNA Complexes*

- April 7–10, 1995, Leopoldina Society, Halle, Germany; Lecture: *Physik des Schens*

- April 8–13, 1995, European Network Meeting on Protein Folding and Stability, San Feliu de Guixols, Spain; Lecture: *Prediction of the Structure of the LIght Harvesting Complex II of Rs. molischianum*

- May 2–7, 1995, Quantum Mechanical Simulation Methods for Studying Biological Systems, les Houches, France; Lecture: *Molecular dynamics and quantum chemistry study of spectral properties, ground and excited state dynamics of retinal in bacteriorhodopsin*

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

- Computational Science and Engineering Steering Committee (CSE);
- Beckman Institute Program Advisory Committee;
- National Research Council Committee on the Future of Computer Science;
- Appointment and Promotion Committee, Department of Physics, University of Illinois;
- Beckman Institute Human Computer Interaction Ad Hoc Committee;
- Beckman Institute External Advisory Committee;

Research personnel of the resource during the past year have participated and/or presented contributions at the following meetings and institutions:

- Mount Sinai School of Medicine, New York, NY (Wriggers, May 1994)
- Edinburgh University, Edinburgh, Scotland (Wallace, May 1994)
- University of Oxford, Oxford, England (Wallace, May 1994)
- Pfizer–Beckman Institute Symposium: Protein Engineering and Design, Beckman Institute, University of Illinois at Urbana–Champaign, Urbana, IL (Xu, June 1994)
- Princeton Lectures on Biophysics, Princeton, NJ (Logunov, June 1994)
- NeXTstep Expo, San Francisco, CA (de la Tribouille, June 1994)
- Neural Networks for Physicists IV, Minneapolis, MN (Hesselroth, Wallace, Zeller, July 94)
- Summer School on Complex Systems, Santa Fe, NM (Tzonev, July 1994)
- IMA Summer Program, Minneapolis, MN (Bishop, Dalke, Hamer, Humphrey, Izrailev, Khardia, Kosztin, Logunov, Nelson, Phillips, Skeel, Wallace, Wriggers, Xu, August 1994)
- Hot Interconnects II, Stanford University, Stanford, CA (Humphrey, August 1994)
- NIH seminar on Management Concepts, Chicago, IL (Budescu, August 1994)
- NSF GCAG, New York University, New York, NY (Skeel, September, 1994)

- National Cancer Institute, National Institute of Health, Frederick, MD (Xu, September 13, 1994)
- 7th Annual Cell and Molecular Biology, Molecular Biophysics Research Symposium, Beckman Institute, University of Illinois at Urbana–Champaign, Urbana, IL (Xu, September 24, 1994)
- Commercial ATM Networks Seminar, Rosemont, IL (Brunner, Phillips, Pütz, Shinozaki, September 1994)
- Biophysical Society, 7th Biophysical Discussion, Airlie, VA (Wriggers, October 1994)
- Advanced Computing Laboratory, Los Alamos National Lab, Los Alamos, NM (Humphrey, October 1994)
- Workshop on Algorithms for Macromolecular Modeling, University of Kansas, Lawrence, KS (Balaeff, Izrailev, Logunov, Skeel, Srinivas, November, 1994)
- Society for Neuroscience Meeting, Miami, FL (Tzonev, November 1994)
- University of Otago, Otago, New Zealand (Wallace, November 1994)
- HPCC retreat, Yale University, New Haven, CT (Bishop, Dalke, Gursoy, Hu, Humphrey, Kale, Nelson, Phillips, Skeel, Srivinas, Wriggers, Xu, Zhou, November 1994)
- Supercomputing '94, Washington, DC (Dalke, Gursoy, Humphrey, Nelson, November 1994)
- Denver NIPS conference, Denver, CO (Tzonev, December 1994)
- Biophysical Society Meeting, San Francisco, CA (Bishop, Humphrey, Logunov, Wriggers, Xu, Zhou, February 1995)
- 7th Annual SIAM Conference on Parallel Processes, (Kale, 1995)
- Columbia University, New York, NY (Zhou, March 1995)
- Bristol–Meyers–Squib, Princeton, NJ (Zhou, March 1995)
- UNC Collaborative Meeting, North Carolina Supercomputer Center, Research Triangle Park, NC (Dalke, Nelson, March 1995)
- Nature: Structural Biology Conference, Structural Biology: The Molecules of Life, Chicago, IL (Baleaff, Hu, Kosztin, Schnitzer, Wriggers, April 1995)

Resource Seminar

The resource has organized a seminar series at the Beckman Institute. During the past year the following outside speakers have presented lectures:

- Prof. Andreas Dress, Department of Mathematics, University of Bielefeld, Germany, August 12, 1994, Lecture: *Methods for analyzing the evolution of biological information*
- Prof. Hartmut Michel, Max–Planck–Institut fur Biophysik, Frankfurt, Germany, August 17, 1994, Lecture: *The structure of the photosynthetic reaction centers from Rhodopseudomonas viridis and Rhodobacter sphaeroides – recent progress*
- Prof. Jiri Jonas, Director, Beckman Institute, University of Illinois at Urbana–Champaign, IL, August 29, 1994, Lecture: *NMR Studies of Pressure Induced Unfolding of Proteins*
- Dr. S. Okazaki, Department of Electronic Chemistry, Tokyo Institute of Technology, Tokyo, Japan, September 8, 1994, Lecture: *An NPT Molecular Dynamics Simulation of a DPPC Phospholipid Bilayer in the Fluid Phase*
- Prof. Joel Berendzen, Los Alamos National Laboratory, Los Alamos, NM, September 12, 1994, Lecture: *Myoglobin Mysteries Made Manifest*
- Prof. Andrew Wang, Department of Cell and Structural Biology, University of Illinois at Urbana–Champaign, IL, September 19, 1994, Lecture: *The Crystal Structures of Gene V Protein (GVP) from Ff Phages: How does GVP Bind Cooperativly to Single–Stranded DNA?*
- Prof. Hisahura Hayashi, Molecular Photochemistry Lab, The Institute of Physical and Chemical Research (RIKEN), Japan, October 3, 1994, Lecture: *Magnetic Field and Magnetic Isotope Effects in Reactions of Heavy Atom–Centered Radicals*
- Prof. Ana Jonas, College of Medicine, University of Illinois at Urbana–Champaign, IL, October 10, 1994, Lecture: *Phospholipid bilayers in tight places: lipoprotein structure and model membranes under high pressure*
- Prof. Antony R. Crofts, Department of Biophysics and Beckman Institute, University of Illinois at Urbana–Champaign, IL, October 17, 1994, Lecture: *Predicting structure of membrane proteins: Cytochrome b of the bc–complex*
- Prof. Benoit Roux, University of Montreal, Montreal, Canada, October 24, 1994, Lecture: *Molecular Dynamics Simulations of the Gramicidin Channel*

- Prof. Manfred Radmacher, University of California at Santa Barbara, Santa Barbara, CA, November 14, 1994, Lecture: *Imaging Proteins with the Atomic Force Microscope*

- Prof. Jin Wang, Department of Chemistry, University of Illinois at Urbana–Champaign, IL, November 21, 1994, Lecture: *Reaction Dynamics of Proteins and Single Molecules in Fluctuating Environments*

- Prof. Ian Robinson, Physics Department, University of Illinois at Urbana–Champaign, IL November 28, 1994, Lecture: *Coherent X–ray Diffraction: Possible Application to Protein Crystals*

- Juergen Koeppke, Max–Planck–Institute for Biophysics, Frankfurt, Germany, January 12, 1995, Lecture: *Toward the Structure of Light Harvesting System 2: Modelling and X–ray data*

- Prof. Jan Hermans, Department of Biochemistry and Biophysics, School of Medicine University of North Carolina, Chapel Hill, NC, January 27, 1995, Lecture: *Application of Free Energy Simulations to Peptide Conformation*

- Prof. Monique Tirion, Department of Physics, Clarkson University, Potsdam, NY January 30, 1995, Lecture: *F–Actin Structure and Dynamics*

- Prof. Ernst Bamberg, Max–Planck–Institut fr Biohysik, Frankfurt, Germany, March 6, 1995, Lecture: *Vectorial Transport in Halorhodopsin and Bacteriorhodopsin*

- Prof. Stephen White, Department of Physiology and Biophysics, University of California at Irvine, Irvine, CA, March 27, 1995, Lecture: *Partitioning of Peptides into Lipid Bilayers and Octanol: First Steps Toward an Experimental Membrane 'Hydrophobicity' Scale*

- Cornelius Weber, Technische Fakultaet, University of Bielefeld, Germany, March 31, 1995, Lecture: *A Model for the Regeneration of the Retinotectal Projection in Goldfish*

- Prof. Isaiah Shavitt, Department of Chemistry, Ohio State University, Columbus, OH, April 3, 1995, Lecture: *Multireference Perturbation Theory and the Calculation of Potential Energy Surfaces*

- Rudi van Drunen, University of Groningen, The Netherlands, April 24, 1995, Lecture: *Molecular Dynamics Simulation on Parallel Computers – New Developments by the Groningen Group*

Bibliography

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[3] Q. Sheng, K. Schulten, and C. Pidgeon. A molecular dynamics simulation of immobilized artificial membranes. *J. Phys. Chem.* Submitted. [Beckman Institute Technical Report TB-95-04].

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