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Annual Progress Report

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Summary of Research Progress

This progress report covers the first year, of an initial five year funding period, in which the Resource operated with full NIH support. Accordingly, the year has been characterized by an expansion of staff, the acquisition of major equipment, and consolidation of Resource activities.

This period has also been marked by the emergence of the second generation of parallel computers, the technology on which the Resource is based. This second generation is distinguished by the considerable degree of convergence, in terms of the programming concepts utilized, and increasing technical sophistication. This necessitates a shift in Resource activities away from proof of concept approaches in parallel computing towards the optimal use of existing machines. This new technology allows a broad base of users to undertake challenging projects which hitherto would have been impossible.

The past year has marked the departure of three of the Resource's founding members (graduate students Klaus Obermayer, Andreas Windemuth and Helmut Heller), who played key roles in establishing the Resource as a pioneer of scientific parallel computing. Several new graduate students, who overlapped with these individuals for a considerable amount of time, have however, matured and become experts in both their respective research areas and computational technology. Three postdocs have joined or are in the process of joining the Resource. The Resource has also hired an excellent programmer and, most importantly, has attracted Dr. Gila Budescu as a competent and strong scientific administrator.

The remaining part of this summary provides an overview of projects described in more detail in subsequent parts of the report. It also presents the research activities in the context of the broader mission of the Resource.

Second Generation of Parallel Computing and its implications for Computational Biology

Presently, we are experiencing a phase of consolidation of parallel computing. The National Centers have acquired, or are in the process of acquiring, large scale parallel machines such as the Kendall Square Research KSR1 and KSR2 machines, Thinking Machines CM-5s, Intel Paragons, Cray C90/t3ds or IBM SP1s amongst others. Though to varying degrees immature, these machines provide performance at the GFLOP level and are being embraced by a much wider user group than earlier parallel computers. Various well-known software packages employed by the biomedical community, particularly in the field of structural biology, are becoming available on these machines. Vendors appear to

be converging to a so-called MIMD computing model, and the majority seek to simplify programming tasks through the provision of shared memory type data allocation.

Resource activities are closely coupled to these external developments and require continuously realigned accordingly. This has several important consequences:

(1) Acquisition of a Scalable Parallel Computer

The Resource has observed the performance of the various machines now becoming available and revised its initial choice of a 16 node partition of a Thinking Machine CM-5 operated by the National Center for Supercomputing Applications. The reasons were severalfold: (i) the difficulty of porting any existing software to the CM-5 during the first six months of operation; (ii) the problem of distinguishing purchase of a machine from effectively purchasing machine time from the National Center for Supercomputing Applications (NCSA) coupled to the fact that the Resource obtained over 67,000 processor hours on the CM-5 as a grand challenge application group; (iii) a decision on the part of NCSA to establish its own computational biology group. Consequently the Resource is in negotiations with several vendors regarding the purchase of a scalable parallel machine. The best candidates currently are a 16 node IBM SP1 or a multi-processor Silicon Graphics machine. Cornell Supercomputer Center is presently installing a 256 node version of the IBM SP1 and the Argonne National Laboratories has a 128 node version. Applications developed at the Resource can, therefore, run with few modifications on these larger machines. Silicon Graphics machines have the advantage of being highly compatible with workstations operated by the majority of researchers in the structural biology community; the largest group of collaborators and users of the Resource. The use of a shared memory model, however, places severe restrictions on the scalability of the architecture; currently the largest prospective version of a parallel Silicon Graphics is limited to 24 processors.

(2) Emerging Roles for the Resource

The role of the Resource as proof of concept pioneers in parallel computing in the biomedical sciences is essentially over. The key issues that must be addressed in the foreseeable future are: (i) the development of parallel versions of widely used molecular dynamics programs; (ii) testing of new algorithms and parallel programming concepts; (iii) the exploitation of massively parallel computers through applications, in particular the aforementioned, developed to solve computationally intensive problems in the biomedical sciences. The Resource continues to strive to achieve these goals. Resource staff are beginning a collaboration with Brünger at Yale on parallelizing the widely used program XPLOR; a collaboration with Board at Duke to develop fast Coulomb force algorithms

is continuing; a new collaboration with Schlick at New York University on Long Time Integration methods has been initiated. Resource staff are particularly active in porting the MD and EGO programs developed by the Resource to the major parallel machines at the National Centers employing the coordination language Charm. To this end the program MD with a parallel version of the fast Multipole Algorithm is being ported to the CM-5. The program EGO, a true MIMD type software package, has been ported from occam 2 to C, and is being ported into Charm thereby permitting its migration to various parallel computers, in particular, the CM-5, the Paragon and the IBM SP1 machines.

Applications

The Resource continues to focus upon projects which satisfy the criteria of being both biological relevant and for which massively parallel computers are essential. These applications include:

1. The simulation of large patches of biological membranes of various lipid compositions which allow to study the solvation of drugs and other biopolymers, the transport of drugs and biopolymers, the immersion of trans-membrane proteins and the association of proteins at the membrane surface.

2. the study of hormone receptors bound to DNA.

3. The study of the development of striate cortex in the macaque and a related study of the development of multi-layered retinotopic representations in the lateral geniculate nucleus (LGN). The latter study involves the development of an atlas which represents the available biological data as well as involves model building to understand the development of the representation in the LGN.

4. The development of NMR microscopy. This activity concentrates presently on the optimization of pulse and gradient sequences, interpretation of data in terms of system geometries and experimental applications.

In conclusion our current activities, in conjunction with our previous work, continue to demonstrate our commitment to the stated aims of the Resource.

Distributed Interactive Molecular Dynamics

The rapid increase in speed and availability of very high performance computers in the past few years, coupled with advances in algorithms such as the Fast Multipole Algorithm has greatly expanded the capabilities of molecular dynamics simulations. Systems of several thousand atoms can now be simulated for timescales on the order of many picoseconds to a few nanoseconds. Relatively soon, the time required to calculate one timestep for small molecules up to even medium-sized protein systems (composed of around $1,000$ to $4,000$ atoms), will become small enough to allow interactive control and display of the dynamics simulation. In anticipation of this, the Resource is developing a system for distributed interactive molecular dynamics, which will allow us to use a local graphics workstation to display and control a molecular dynamics calculation being run on a remote supercomputer or high-performance workstation. This project is carried out in collaboration with Rick Kufrin (supercomputer application specialist, NCSA). The goals of this project are

- provide basic molecular visualization and display.
- provide a direct connection to remote computers running molecular dynamics simulations, allowing for control and direct interaction with the remote calculations.
- provide support for several display and input devices.

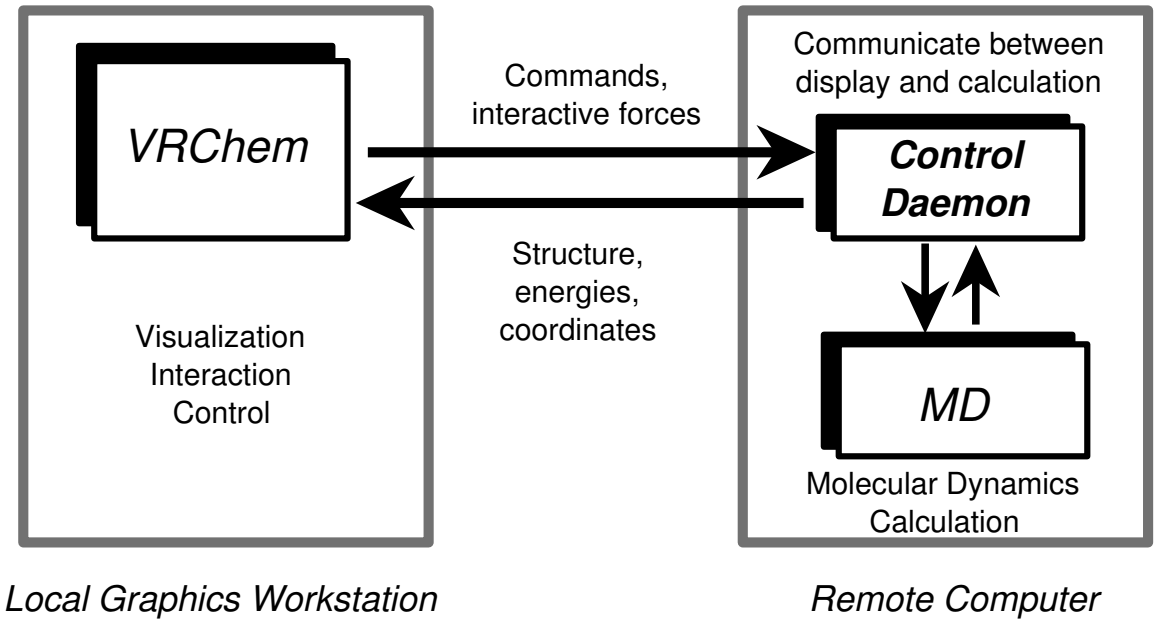

Figure 1: Overview of VRChem, a system for distributed interactive molecular dynamics.

Figure 1 shows an overview of VRChem, a program for interactive molecular dynamics. VRChem accomplishes the first of our two goals by implementing a *distributed* system for calculating and visualizing molecular dynamics simulations. On a local graphics workstation, a visualization and control process is responsible for displaying the molecular system of interest, via a graphical user interface and molecular renderer. Further, this program provides menus for controlling the initiation, status, and termination of molecular dynamics simulations run on a remote computer. On a remote supercomputer or high-performance workstation (which could be the same as the local graphics workstation), two processes are present: MD, the molecular dynamics simulation software itself, and a Control Daemon, which is responsible for mediating communication between the VRChem process and the MD process. The user initially selects what remote machine to use, and which dynamics package to run; on the remote computer, the Control Daemon is started, which loads the MD process, and buffers data and commands passing between computers. With the connection established and simulation initiated, the user now has full interactive control of the simulation – energies and coordinates are sent over the network from the MD program to VRChem as they are calculated, and VRChem has control over simulation status, and dynamical parameters such as temperature, velocity rescaling/reassignment frequency, or timestep size. Remote simulations can be started from the local graphics workstation, or, since many supercomputer system impose time limits on interactive jobs, can be started initially as a batch command on the remote machine and later "attached to" by VRChem.

The third goal of this project is realized by using an object-oriented design for the local workstation program, to allow many different display devices to be selected for use, as well as different input devices, such as a mouse or a spatial tracking system, a device which measures the three-dimensional position of a pointer. Of particular interest and excitement for the project as a display device is a stereo projection system, coupled with a spatial tracking device, which the Resource is currently installing. This system offers many advantages over other alternate display systems, such as head-mounted virtual reality displays or the Fake Space Labs Boom, which suffer from low resolution, poor color, and being inherently limited to a single viewer. The projector provides stereo images in full color and the same resolution as the graphics workstation uses to drive the projector; by wearing glasses equipped with special liquid-crystal lenses, several researchers can view three-dimensional images of molecular assemblies simultaneously. When a remote molecular dynamics simulation is being displayed on-line, the ultimate goal of this system is to allow the user to interactively add perturbative forces to the simulation through use of the three-dimensional pointer, which will be communicated back to the remote system and included in the dynamics. One immediate application of such a system is the determination and refinement of water molecule structures within a protein.

An early prototype of the system has been developed in the past year and was demon-

strated at the SIGGRAPH '92 exhibition in Chicago, Illinois. This program did not implement the Control Daemon, but did demonstrate the feasibility of remote computation and network communication for molecular dynamics simulations. The local graphics visualization software (VRChem) has been developed for use on Silicon Graphics workstations, and support included for display on the workstation monitor, stereo projectors, the Fake Space Labs Boom, and the VPL Eyephone head-mounted display. We are currently adding network communication code, initially targeting the Connection-Machine 200 and high-performance workstations for remote computation, using the MD molecular dynamics software developed by the Resource. Once initial testing is complete, we plan to include the capability of using the molecular dynamics program EGO also developed by the Resource, on several platforms including the CM-5 and the Parsytec GC.

Molecular Modelling of Biological Membranes

Many important reactions of the living cell involve biopolymers associated with cell membranes. To be effective drugs usually need to pass through cell membranes to reach their target, a requirement which leaves many candidate drugs in pharmacological laboratories eventually ineffective. For example, many existing HIV protease inhibitors are ineffective since the compounds synthesized are either poorly solvable in cell membranes or cannot cross these membranes. Until recently efforts to use molecular modelling tools to predict the behavior of drugs in membranes or to understand the interaction of membrane lipids with proteins were impeded by the size of lipid bilayer/water systems which constitute the smallest, yet meaningful membrane lipid environment. For example, a membrane patch of size 85 Å×100 Å together with several layers of water (Fig. 2) involves about 30,000 atoms and needs to be simulated for time periods of a nanosecond or longer. Until recently such time scales and system size would have required years of computer time on supercomputers such as the Cray 2.

Researchers at the Resource have invested several years of effort in methodological development to permit modelling of large membrane patches. These efforts have focused on the use of massively parallel computers on the one hand and on improvements of the numerical algorithms on the other. Resource staff utilize a self-built parallel computer dedicated to modelling membranes and have collaborated with John Board at Duke University to develop algorithms which accelerate the evaluation of forces acting between biopolymers for systems of 30,000 or more atoms by approximately two orders of magnitude.

These efforts have allowed Resource researchers and collaborators to simulate in a calculation the dynamics of a patch of membrane large enough to serve as a natural environment for drug transport. This simulation permits a whole transmembrane protein, bacteriorhodopsin, be embedded in the membrane. The patch modelled consisted of 200 molecules 1-palmiotoyl-2-oleoyl-sn-glycero-3-phosphatidylcholine together with 5483 water molecules. In the first phase of these investigations the researchers established that the computer model agrees well with observed membrane properties like lipid self-diffusion coefficients, so-called NMR order parameters measuring the average orientation of all bonds of the lipid chains and the distribution of molecular groups and water across the membrane.

Resource staff have recently been joined by a medicinal chemist who has developed chromatography surfaces (Immobilized Artificial Membranes, IAM) that mimic the lipid environment of cell membranes. The aim of the collaboration is to develop optimal IAMs for model studies of lipid drug and lipid protein interactions. Using this approach it will be possible to judge membrane solubility and transport properties for any given substance in the laboratory.

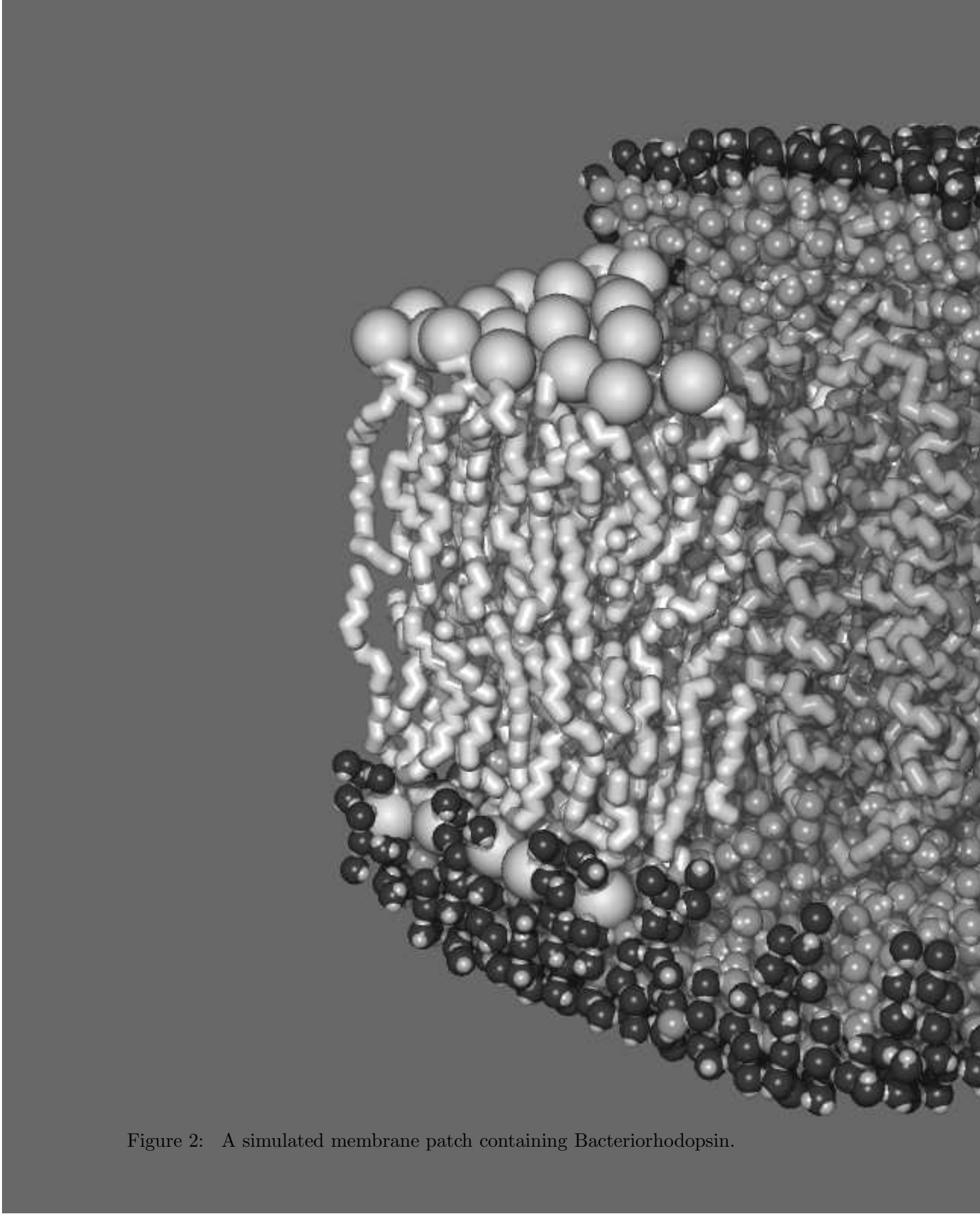

Figure 2: A simulated membrane patch containing Bacteriorhodopsin.

Molecular Dynamics of Bacteriorhodopsin Retinal Analogues

Bacteriorhodopsin (bR), a protein found in the membrane of *Halobacterium Halobium*, functions as a light-driven proton pump which drives ATP synthesis. The protein contains a retinal chromophore bound via a protonated Schiff base linkage to a lysine group roughly in the middle of bR. In order to understand the major driving forces of the proton pump cycle in bR it is essential to understand the detailed structure of the active site of this protein as well as the particular role of the different groups constituting the active site. Taking into account the complexity of the problem, one can only achieve the desired results by combining experimental and theoretical approaches.

To pursue this strategy, we have been collaborating extensively this past year with Dr. Mordechai Sheves, a visiting professor from the Weizmann Institute in Israel. Doctor Sheves is an organic chemist who has been working with the proteins belonging to the rhodopsin family for many years. He has synthesized a few dozen retinal analogues and has conducted hundreds of experiments with these synthetic compounds. We have been supplementing the experiments with an extensive theoretical study by means of molecular dynamics. All simulations used the same parameters, and were done on either a Cray-2 operated by NCSA, or Silicon Graphics workstations operated by the Resource. Every obtained structure was scrutinized using the conventional visualization package Quanta as well as the program VRChem developed by the Resource.

Many experiments have shown the crucial importance of structured water in monitoring the proton transfer through control of the pK values of the retinal Schiff base as well as other groups participating in this process [1]. Inspired by these experiments, we carried out calculations of the pK values and the proton transfer affinities of a few retinal analogues in complexes with water molecules. Both techniques of energy minimization and molecular dynamics were used in these calculations. In order to achieve better agreement with experiment, various possible structures for the analogue-water complexes were tested, with the number of water molecules and their initial spatial orientation being varied. Such an extensive search has led us to our conclusions about the most probable location of water molecules in the active site of bR.

Based on the calculations described above and on the experimental information available [2], we were able to place the important water molecules inside the active site of Bacteriorhodopsin near the retinal Schiff base. After a total of three- hundred picoseconds of molecular dynamics, required for accurate positioning of water molecules and final equilibration, the newly refined active site of bR has been obtained. We further tested the new active site by checking the effect of different modifications of the retinal Schiff base and comparing simulations with the analogue experiments [3, **?**]. Particular attention has been paid to the substitutions in the vicinity of the NH group and in the ring component of retinal. Careful analysis of the equilibrated modified structures has

revealed remarkable agreement with experiment. This has convinced us of the correctness of our new refined structure of Bacteriorhodopsin.

Following determination of this new refined ground-state structure of the active site, we proceeded with the proton pump cycle itself. Simulation of the conventional all-trans (light adapted) cycle at room temperature was complemented by simulation of the 13,15-cis (dark adapted) cycle as well as simulation at low (liquid nitrogen) temperatures. J and K states of the photocycle were obtained through the combination of conventional molecular dynamics calculations with special isomerization potentials applied to the retinal molecule to simulate photo-isomerization. The long-time (on the order of a few microseconds) transitions from K to L and from L to M states were modelled by means of simulated annealing [4, 5].

Our new simulations of the photocycle have confirmed the previous hypothesis about the co-rotation around 13-14 and 14-15 bonds during the initial photo-isomerization step [6]. Combination of the well-refined bR active site with the variety of isomerization simulations has also allowed us to get a better insight into a number of phenomena which are poorly understood so far. This refers to such phenomena as the absense of the M state in the case of the 13,15-cis cycle, leakage from the 13,15-cis to the all-trans cycle, as well as an apparent discrepancy between previous simulations done at room temperature compared to experiments done at low temperatures.

Interaction of phospholipase A_2 with membranes

Extracellular phospholipase A_2 is a small soluble enzyme which binds to biological membrane surfaces and digests the lipid molecules in the membrane-water interface. It has been a subject of extensive experimental (for review see [7]) as well as theoretical studies [8, 9]. Chemical studies as well as the X-ray structures solved for a few species show that the enzyme has a catalytic center similar to a well known class of enzymes–serine proteases. When the lipid substrate binds into the enzyme, the *sn*-2 ester bond is hydrolyzed. The reaction produces fatty acids and lysophospholipids. These reaction products have important physiological roles in the inflammation process [10], and gives phospholipase A_2 considerable pharmaceutical importance. Interaction of the enzyme with lipid vesicles has also been studied. The enzyme associates with the membrane surface at proper conditions, and reacts at a speed much higher than when monomeric substrate is present [11]. Mechanisms including dimerization of the enzyme or desolvation of the enzyme-membrane microinterface have been suggested to explain the high activity of the enzyme on membrane surfaces. Phospholipase A_2 is an excellent model for study of protein–membrane interactions.

In the progress report for budget period 8/01/91–7/31/92, we have reported a preliminary simulation for bovine pancreatic phospholipase A_2 with a piece of membrane monolayer. Our intention was to study how the enzyme interacts with membrane head groups, and the effects of binding to the conformation and dynamics of the enzyme and the lipid. Analysis of the data indicates that the dynamics of the enzyme, on the time scale of about 100 ps, is affected by the binding. Figure 3 shows the average fluctuation of the protein C_α atoms calculated from a 50 ps molecular dynamics trajectory; the fluctuation calculated from the X-ray B factor is also shown for comparison. Motion of the two flexible loops of the protein is damped on the membrane interface.

Simulations were carried out for the human synovial phospholipase A_2, for which the X-ray structure has been recently solved, at a later stage. Two membranes, the dilauryl phosphotidylethanolamine (DLPE) and dimiristoyl phosphatidylcholine (DMPC), were used in the simulation for comparison. It is experimentally known that the human synovial phospholipase A_2 has a higher affinity for membranes with PE head groups compared to PC head groups. Both the DMPC and DLPE lipids in the enzyme-membrane interface show a smaller average angle between the PN vector (phosphorous to ammonium or choline nitrogen) and the bilayer surface as compared to the lipids in pure membrane. Such an effect on lipid head group conformations (they orient more parallel to the membrane surface in the enzyme-membrane interface) is found in all simulations. This conformation change could be induced by the positively charged protein or the desolvation of the lipid head groups. It would also expose more negatively charged groups of the lipid to form stronger interaction with the positively charged enzyme.

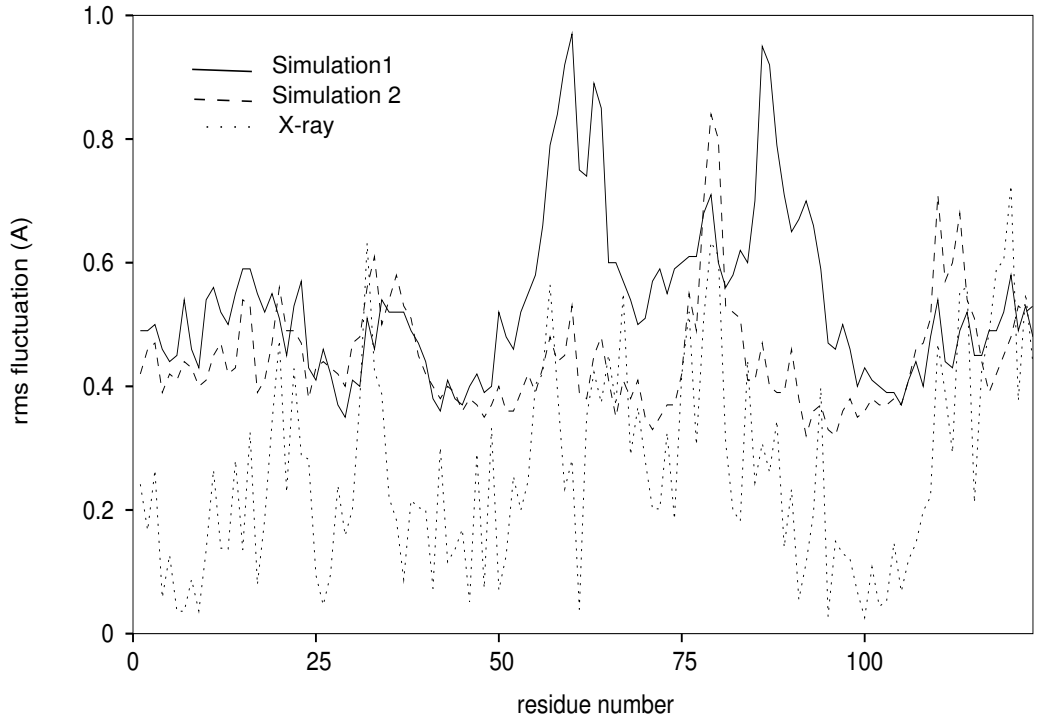

Figure 3: r.m.s fluctuations of the Cα atoms of bovine pancreatic phospholipase A_2 as compared to X-ray B-factors. Simulation 1 is carried out in solution whereas simulation 2 is on membrane surface.

However, it is shown in previous simulations that the conformations of lipid head groups are quite sensitive to the cutoff radius used for electrostatic interactions. A 12 Å cutoff has been used in previous simulations. Using cutoff greatly reduces the computational overhead but can also generate artifacts, especially in membrane systems. To illustrate such effects and to obtain a properly equilibrated DLPE membrane, we have simulated a DLPE bilayer consisting of 202 lipid molecules. The surface density was chosen to correspond to the membrane in the liquid crystalline phase. It is shown that the potential difference between the membrane hydrocarbon phase and the bulk aqueous phase is very sensitive to the cutoff used. Recently, Alper et al have also shown that proper treatment of long range electrostatic interaction is important for studying the behavior of water in membrane-water interfaces [12]. We plan to use the program MD with no cutoff and the properly equilibrated membrane for future studies. In order to speed up calculation for very large systems, MD has implemented the fast multipole approximation and distance class algorithms for Coulomb interactions. Because of these recent advances in software, we are now able to simulate systems as large as 35,000 atoms with reasonable speed even on workstations without loss of accuracy in long-range interactions.

Geometry of Orientation and Ocular Dominance in Striate Cortex

The primary visual cortex, or striate cortex, is a principal destination for information regarding the visual field. Studies by Hubel and Wiesel have shown that although most cells in the striate cortex are binocular their response to visual stimuli favors input from one eye or the other; a phenomenon referred to as ocular dominance. Hubel and Wiesel also demonstrated that cells within the cortex are tuned for a particular orientation of stimuli and that cells selective for either a particular eye or orientation are grouped together in slabs that run vertically from pia to white matter. Based upon their observations these authors suggested that slabs of iso-orientation and ocular dominance intersect at some consistent angle.

Efforts to substantiate this hypothesis have until recently been impeded by the lack of a suitable experimental technique. Differential video imaging techniques now make it possible to address the issue by providing high resolution maps of orientation preference and ocular dominance from the same region of cortex *in vivo*. The maps of orientation thus revealed indicate that cells preferring similar orientation are indeed organized as slabs. They also reveal that these slabs are shorter than had previously been expected and are restricted to patch-like regions 0.5 mm-1 mm across. Such patches are particularly abundant between the centers of adjacent ocular dominance columns, where the short iso-orientation slabs within them appear to intersect the borders between adjacent ocular dominance columns at steep angles. The apparent orthogonality between ocular dominance and orientation slabs has been described briefly in some of our previously published work [13, 14]. We have developed upon this work by applying several quantitative measures to describe the spatial organization of the cortex.

This analysis leads us to conclude that: 1) orientation preferences are organized laterally by at least two competing themes that generate linear and non-linear compartments in complementary regions of cortex, 2) that orientation preferences repeat at slightly longer intervals in directions perpendicular to the ocular dominance columns than in directions along them and 3) that within the linear zones short slabs of iso-orientation may be discerned that intersect the borders of ocular dominance columns at steep, essentially perpendicular angles.

Models of Lateral Geniculate Nucleus Development

Each half of the brain contains a structure known as the lateral geniculate nucleus (LGN). This area receives visual input from both eyes and sends projections to the cerebral cortex, principally, the striate cortex. In primates the LGN consists of several distinct layers of neurons separated by intervening layers of axons and dendrites. Each layer more or less maps the projections from retinal cells in a topographic fashion. Figure 4 illustrates sample cross-sections of the LGN of the rhesus monkey (*Macaca mulatta*) provided by J. Malpeli, an experimental psychologist at the University of Illinois. Resource staff are currently pursuing a number of theoretical investigations into the structure and function of the LGN in collaboration with Dr. Malpeli and his research group.

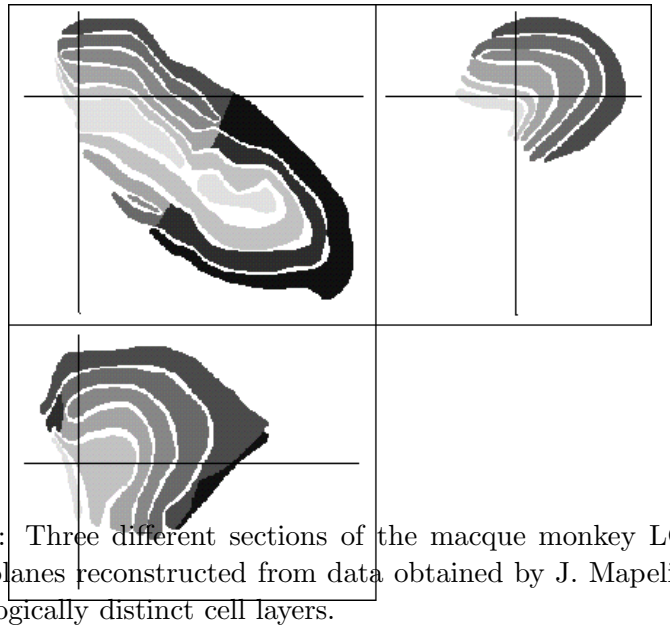

Figure 4: Three different sections of the macque monkey LGN taken through perpendicular planes reconstructed from data obtained by J. Mapeli. Different shades code for morphologically distinct cell layers.

Only morphological data for the layers of neurons is shown in Figure 4. Dr. Malpelli has also obtained data on the topographic mapping of the retinas in each layer using *in vivo* micro-electrode recordings techniques [15]. This body of data, though incomplete, provides the most detailed description available regarding the structure of the LGN in any

species. The form of the layers and the embedded topographic maps have only been reconstructed along certain cross-sections at discrete points. One project currently being pursued by group members is to complete a three-dimensional atlas of the rhesus monkey LGN through the reconstruction of the structure of the LGN at locations between the measured data points. These results will be included in a brain atlas database being created at the Lawrence Livermore National Laboratory which will be available for consultation by interested parties. The result will also be utilized by resource members who are currently modelling the formation of the LGN using two different but complementary techniques.

The first method, known as simulated annealing, involves minimizing a cost function defined, in this particular case, in terms of the distances between terminals of retinal cells projecting to the LGN. Minimization of this function drives the model to locally stable states. Through gradual adjustment of a particular parameter, technically known as the *effective temperature*, crystalization corresponding to the observed structure of the LGN is obtained. Preliminary results show that this approach captures some of the general features of the observed data. For example, in some simulations the presence of the optic disc, which corresponds to the blind spot of the eye, forces the transition between a six- and a four-layer region to occur at the position of the optic disc in the retinotopic map.

A three-dimensional neural network model of LGN formation which describes the gradual emergence of the observed laminar structure as an unsupervised learning process is also being developed. In this approach the neighborhood relations between the retinal cells are used to induce the topographic character of the resulting mapping. The model employs self-organizing feature maps of the type studied extensively at the Resource by Ritter *et al.* [16]. The computational resources required by this approach are considerable; thus this model is being implemented on large parallel computers, principally CM-2 and CM-5 Connection Machines.

This approach is still in its initial phase, however, it is our intention to explore the following issues:

- Which properties of the system determine its general laminar structure
- What the function of the optic disk is in the retinas for the six to four layer transition in the LGN
- How this transition differs in two and three dimensions
- Under which conditions will the disturbance introduced by the optic disk will propagate beyond its actual limits

Comparison with data regarding the LGN obtained from other species will be used to establish the validity of the approach and to test if it can explain differing morphologies. Through the use of the macaque LGN as a model system we hope to develop greater understanding of the general principles underlying the development of structures of the brain such as the LGN.

BRTP UNIT: T

TITLE: Distributed Interactive Molecular Dynamics

KEYWORDS: graphics,network,visualization,remote computation

AXIS I: 9 11

AXIS II: 42

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DEGREE1: MS
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NONHOST1:

INVEST2: R. Kufrin
DEGREE2: BS
DEPT2: National Center for Supercomputing Applications
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% BRTP $: 12

ABSTRACT: We are continuing development of an interactive environment for molecular dynamics simulations, designed to allow a researcher to visualize and control a dynamics simulation on a remote supercomputer or high-performance workstation. To accomplish this, we are developing a system consisting of a local graphics workstation running a visualization and control program, a communication broker program running on the desired remote host, and a molecular dynamics package capable of receiving data from/sending data to the local graphics workstation via the communication broker. A user will be able to start and interactively control dynamics simulations running concurrently on the remote host, and also to attach to already-running jobs. Support for several display systems is provided, in particular a large-screen stereo projection facility and 3D pointer device which will allow several researchers to simultaneously view and interact with stereo images of molecular systems.

BRTP UNIT: T

TITLE: Accelerated Molecular Dynamics Simulation with the Parallel Fast Multipole Algorithm

KEYWORDS: Molecular Dynamics, Fast Multipole Algorithm, Parallel Processing

AXIS I: 2 9

AXIS II: 42 74

INVEST1: John A. Board
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DEPT1: Electrical Engineering
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% BRTP $: 4

ABSTRACT: The fast multipole algorithm (FMA) has been implemented on scalar and parallel machines and has been incorporated into a molecular dynamics program to permit rapid evaluation of the non-bonded interactions in simulations of biological macromolecules. The algorithm has been compared with the direct method of evaluating the Coulomb force field (explicit summation over all atom pairs) and was found to be highly accurate while providing a ten-fold increase in speed for a 24,000 atom system on a scalar processor (workstation). Because the FMA runtime grows linearly as the size of the simulated molecular system increases, we expect the benefit to increase as larger molecules are studied. The algorithm has also been shown to run efficiently in parallel on modest numbers of processors (16). We will investigate various optimizations of the FMA on larger parallel systems (64 processors and beyond) and will incorporate it into an additional MD program (C-EGO) used for production computations at the Resource.

BRTP UNIT: T

TITLE: Parallel Molecular Dynamics Program for MIMD-type Computers

KEYWORDS: Transputers, CHARM coordination language, CM-5, network of workstations

AXIS I: 9 11

AXIS II: 42 70

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% BRTP $: 4

ABSTRACT: In the previous funding period, the performance of EGO (OCCAM version running on the Transputers) was evaluated. The evaluation was done for smaller molecules of about 500 atoms. In this funding period, further performance evaluation was carried out for a membrane bilayer. This evaluation confirmed that the conclusions we had drawn about the performance of EGO from the previous study were valid for much larger molecular systems.

In the previous funding period, we had begun converting the EGO code written in Occam to C. EGO-C (C version of EGO) was first tested on the CM-5 machine. Later in the same funding period, and through to the current funding period, we have tried converting EGO-C to EGO-Charm (Charm version of EGO). Charm is a machine-independent parallel programming language, which currently runs on shared memory machines, such as Encore Multimax, Sequent Symmetry and Balance, distributed memory machines, such as Intel iPSC/2 and i860, NCUBE/2, and

networks of UNIX workstations, and UNIX-based uniprocessor machines. EGO-Charm is very similar to EGO-C, except all message passing is done in an asynchronous manner in Charm. EGO-Charm runs on shared memory machines, such as the Encore Multimax. It also runs on a network of UNIX workstations, though the performance needs to be improved considerably. In this funding period, Charm is being ported to the CM-5 and Intel Paragon machines. After Charm has been ported to these machines, the EGO-Charm port to the CM-5 and Paragon should be considerably simplified.

BRTP UNIT: T

TITLE: Algorithms for Molecular Dynamics

KEYWORDS: numerical algorithms, symplectic integration.

AXIS I: 2 9

AXIS II: 42 74

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DEGREE3: MS
DEPT3: Computer Science
NONHOST3:

INVEST4: Jeffrey Biesiadecki
DEGREE4: BS
DEPT4: Computer Science
NONHOST4:

INVEST5: Benedict Leimkuhler
DEGREE5: PhD
DEPT5: Mathematics
NONHOST5: Univ. of Kansas

% BRTP $: 8

ABSTRACT: We have begun rewriting the molecular dynamics program PMD (parallel MD) developed at the Resource to run on the CM-5 and to use the superior velocity form of the Verlet integration method. We are running on the CM-5 a much smaller Lennard-Jones code that is being used extensively to test new integration methods. These experiments show that the Verlet method is much superior to other methods proposed for molecular dynamics but there are other newly proposed "symplectic" methods that might have an edge. Also, we have done a thorough study of multiple time stepping and variable stepsize methods (distance class techniques) on model problems and have identified two possible dangers of this technique. Finally we have shown that symplectic integration methods exactly conserve angular momentum in a variety of situations.

BRTP UNIT: C

TITLE: Interaction of Phospholipase A_2 and membrane surface

KEYWORDS: phospholipase A_2, phosphotidylethanolamine, solvation energy, free energy calculation, drug design

AXIS I: 5 6

AXIS II: 74f,h

INVEST1: Feng Zhou
DEGREE1: BS
DEPT1: Biophysics
NONHOST1:

INVEST2: Robert B. Hermann
DEGREE2: PhD
DEPT2: Biotechnology
NONHOST2: Eli Lilly and company

% BRTP $: 8

ABSTRACT: Interaction of bovine pancreatic and human synovial phospholipase A_2 with biological membrane surfaces is studied by molecular dynamics. The interaction of the enzyme with the membrane surface, the dynamics properties of the protein and lipid head groups are analyzed. A different orientation of the lipid head groups in the enzyme-membrane system is observed compared to a pure membrane, which awaits confirmation by further studies with better algorithms employed. Deprotonation of DLPE is suggested to be important in binding the highly positively charged human synovial phospholipase A_2. The program XPLOR was used in previous simulations with a 12 Å cutoff for nonbonded interactions.

In order to describe the electrostatic interactions of the system more reliably, a DLPE membrane was constructed and simulated using the program MD. The program employs fast multipole and distance class algorthms and gives reasonable performance even for very large systems. Cut-off of Coulomb forcesaffects the polarization of water in the interface and overestimates the calculated membrane dipole potential. We intend to carry out further studies of the enzyme-membrane system using the MD program and the POPC and DLPE membranes constructed by Resource staff. Free energy calculations are planned for smaller systems to study specific questions related to enzymatic kinetics.

BRTP UNIT: C

TITLE: Molecular Dynamics Study of Bacteriorhodopsin

KEYWORDS: bacteriorhodopsin, membrane protein, br, retinal, dynamics, retinal analogues

AXIS I: 2 6 7A

AXIS II: 74H

INVEST1: W. Humphrey
DEGREE1: MS
DEPT1: Physics
NONHOST1:

INVEST2: I. Logunov
DEGREE2: MS
DEPT2: Chemical Physics
NONHOST2:

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

% BRTP $: 12

ABSTRACT: Bacteriorhodopsin (bR), a protein found in the membrane of Halobacterium Halobium, functions as a light-driven proton pump which drives ATP synthesis. The protein contains a retinal chromophore bound via a protonated Schiff base linkage to a lysine group roughly in the middle of bR. Several experimental studies of retinal analogues done in the group of Dr. M. Sheves of the Weizmann Institute in Israel have revealed many interesting phenomenon related to the proton pump cycle of bR. As a further probe of these effects, we have conducted molecular dynamics studies of several of these retinal analogues, to try to understand the mechanisms behind observed changes in the proton pump cycle, and observed spectroscopic shifts from the original ground state. To accomplish this, we have first placed several water molecules near the active binding site of retinal, equilibrated this system and compared the resulting ground state structure to the known experimental structure and data. Following this, we have modified the ground state to the same structures used in the experiments of Dr. Sheves, equilibrated the result, and simulated the modified structures. All simulations used the same parameters, and were done on either

a Cray-2 operated by NCSA, or on Silicon Graphics workstations operated by the Resource. We compare the results to experiment by studying changes in torsional bond angles, changes to hydrogen-bond structures, and differences in charged group distances from the retinal active site.

BRTP UNIT: C

TITLE: Molecular Modelling of Biological Membranes

KEYWORDS: lipid bilayers, membrane structure, membrane transport, POPC membrane

AXIS I: 6 9

AXIS II: 74f,h

INVEST1: Helmut Heller
DEGREE1: Diplomphysiker
DEPT1: Physics
NONHOST1:

INVEST2: Charles Pidgeon
DEGREE2: PhD
DEPT2: Medicinal Chemistry
NONHOST2: Purdue University

% BRTP $: 4

ABSTRACT: We have constructed and simulated a membrane-water system which consists of 200 molecules of 1-palmiotoyl-2-oleoyl-sn-glycero-3-phosphatidylcholine forming a rectangular patch of of a bilayer and 5483 water molecules covering the headgroups on each side of the bilayer. The total number of atoms is approximately 27,000. The lateral dimensions of the bilayer are 85 Å×100 Å and the distance between the bilayer surfaces as given by the average phosphorous to phosphorous distance is 35 Å. The thickness of each water layer is up to 15 Å. In all we simulated 263 ps of the dynamics of the system. To prevent system disintegration, atoms within 5 Å from the surface were harmonically restrained and treated by Langevin dynamics, forming a stochastic boundary. Interior lipids and water molecules were unrestrained. The first 120 ps of the dynamics calculation were used to equilibrate the system and to achieve a low internal pressure. We performed two simulations for analysis, simulation I of the system that resulted from the equilibration, simulation II of the system after an increase of the area per head group from 46.3 Å^2 to 70 Å^2. For both simulations I and II we determined the internal pressure, the lipid self-diffusion coefficients, the order parameter profile, the distribution of molecular groups, and other properties. The observables extracted from simulation II are in good agreement with experiments on bilayers in the liquid crystal phase. The structure resulting from this work has been used for molecular dynamics investigations

of drug transport in membranes, for the study of trans-membrane protein-lipid interaction (bacteriorhodopsin) and for the association of human phospholipase A_2 with the membrane.

An investigation of chromatography surfaces (Immobilized Artificial Membranes, IAM) that mimic the lipid environment of cell membranes has recently begun. The aim is to complement synthetic work at the Purdue laboratory of Pidgeon, to employ IAM's for model studies of lipid drug and lipid protein interactions and to contribute through rational molecular design to the development of suitable IAM assays to test membrane solubility and transport of biochemically active substances.

BRTP UNIT: T

TITLE: Molecular Dynamics Study of a Sequence Specific Protein-DNA Complex in an Aqueous Environment

KEYWORDS: protein-DNA interaction, nuclear receptor hormones, GR-DBD, GRE

AXIS I: 9

AXIS II: 74e,g,h

INVEST1: Thomas C. Bishop
DEGREE1: MS
DEPT1: Chemistry
NONHOST1:

INVEST2: Ann Nardulli
DEGREE2: PhD
DEPT2: Physiology and Biophysics
NONHOST2: nonhost

INVEST3: John Katzenellenbogen
DEGREE3: Phd
DEPT3: Chemistry
NONHOST3: nonhost

% BRTP $: 8

ABSTRACT: The crystal structure of the DNA-binding domain of the glucocorticoid receptor complexed with DNA has been made available to us by Sigler et al [17]. When the glucocorticoid receptor binds to DNA it dimerizes, and each monomer subunit of the receptor forms specific interactions in the major groove of the DNA. The target DNA consists of symmetric half-sites separated by a three base pair sequence of DNA. For the crystallographic analysis an additional base pair has been included in the central three base pair spacing to create an oligonucleotide with exact symmetry. This additional base pair, however, has offset the relationship between the receptor dimer and the DNA such that one monomer subunit forms specific interactions with its corresponding DNA half-site and the other monomer subunit forms non-specific interactions with a discrepant DNA half-site.

In order to construct the consensus DNA target, the molecular dynamics program X-PLOR has been used to remove the additional base-pair spacer from the DNA. The separate segments of DNA which resulted were aligned and reconnected such

that each could make specific contacts with the receptor. The system has become a naturally occurring, perfect palindrome, complexed with the DNA binding domain of the glucocorticoid receptor. In order to simulate the natural environment, the protein and DNA have been encapsulated in an ellipsoid of water consisting of approximately 3,000 water molecules. The dimensions of the ellipsoidal axes are 60 Å×60 Å×80 Å, and a harmonic well potential is applied to any atom which wanders beyond this boundary. All hydrogen atoms are represented explicitly.

Energy minimization, equilibration and dynamics have been conducted using the and the following properties of the system have been evaluated: DNA parameters including major and minor groove width, twist and bending of the helical axis; hydrogen bonding between receptor and DNA, and the correlation to bending; and orientation of alpha helix axes of the receptor in comparison to DNA helical axis.

All computations were done on a Parystec GCel-64, a 64-node parallel computer based on the INMOS T805 transputer. The simulation used the dynamics program EGO, which utilizes a double ring topology for calculation of pair interactions, is compatible with X-PLOR I/O and employs the CHARM force field [18]. The conformational and hydrogen bonding analysis has been done using the analysis package MD Toolchest [19].

Currently, a collaboration with Prof. Ann Narduli and Prof. John Katzenellenbogen is being carried out in which the DNA binding domain of the glucocorticoid receptor will be computationally mutated to form the DNA binding domain of the estrogen receptor. The estrogen receptor is a member of the same family of nuclear hormone receptors and exhibits a high degree of structural and sequence homology with the glucocorticoid receptor. The collaboration with Prof. Ann Narduli and Prof. John Katzenellenbogen was initiated because their success in experimental studies of the estrogen receptor will undoubtedly serve as a complement to the theoretical studies.

BRTP UNIT: C

TITLE: Long Time Protein Dynamics

KEYWORDS: normal mode analysis, Brownian dynamics simulation, hydrodynamic model, friction coefficient, memory function, Rouse-Zimm approximation.

AXIS I: 9

AXIS II: 74h

INVEST1: Dong Xu
DEGREE1: MS
DEPT1: Physics
NONHOST1:

INVEST2: Karl Freed
DEGREE2: PhD
DEPT2: James Franck Institute
NONHOST2: University of Chicago

INVEST3: Xiao-Yan Chang
DEGREE3: MS
DEPT3: James Franck Institute
NONHOST3: University of Chicago

INVEST4: Konstantin Kostov
DEGREE4: MS
DEPT4: James Franck Institute
NONHOST4: University of Chicago

% BRTP $: 4

ABSTRACT: In order to conduct long time dynamics simulations of biomolecules,slow motions and fast motions of the system were analyzed, attempting to predict the most relevant degrees of freedoms of slow motion. With this information a longer integration timestep could be applied.

Projecting the trajectories of all the internal coordinates versus time by the orthogonal transformation matrix diagonalizes the coordinate–coordinate correlation matrix. Although the Hamiltonian of the biopolymer is far from quadratic, normal mode motion superimposed on a random background was obtained. The periods of the normal modes are well defined for low frequencies, but the periods are lost in

random noise for the high frequencies. For the well-defined low frequencies, it was found that the amplitudes were almost the same as the corresponding eigenvalues.

Currently, we are collaborating with Prof. Karl Freed and his graduate students Xiao-yan Chang and Konstantin Kostov in University of Chicago. Prof. Freed's group is currently studying an alternate method, known as the hydrodynamic model, which may allow for much longer time correlation in a relatively short dynamics simulation. This method has been successfully used for polymer and small peptide simulation by Prof. Freed's group. We are attempting to combine our normal mode technique with this hydrodynamic model. In this collaboration, we are solving the problem of long time protein dynamics in the following sequence:

1. one dimensional local motion knowing the detail pathway, e. g., aromatic ring rotations;
2. one dimensional dramatic collective motion knowing the collective pathway, like domain/interdomain motion;
3. multi-dimensional motion without knowing the pathway, such as peptide/protein folding in solvent.

BRTP UNIT: C

TITLE: Geometry of Orientation and Ocular Dominance Columns in Monkey Striate Cortex

KEYWORDS: neurophysiology, self-organizing maps,

AXIS I: 9 21

AXIS II: 41 77 84

INVEST1: K. Obermayer
DEGREE1: PhD
DEPT1: Physics
NONHOST1:

INVEST2: G. G. Blasdel
DEGREE2: PhD
DEPT2:
NONHOST2: Harvard Medical School

% BRTP $: 8

ABSTRACT: In addition to showing that cells in striate cortex are selective for ocular dominance and orientation, Hubel and Wiesel demonstrated that these response properties are organized in slabs, a fraction of a millimeter in width, that extend vertically through all layers. They also suggested that slabs of ocular dominance and orientation intersect at right angles. Through advances in optical imaging it is now possible to test this prediction directly. We have quantitatively analyzed the maps of orientation that are obtained with this approach and conclude that preferences for orientation are organized according to two competing schemes. In the first, changes occur linearly along single axes, forming well defined iso-orientation slabs along the way. In the other, they rotate by 180° along closed paths, forming singularities at their centers. Quantitative comparisons with the maps of ocular dominance reveal that where orientation preferences change linearly the short slabs of iso-orientation formed intersect the ocular dominance columns at steep, essentially perpendicular, angles.

BRTP UNIT: C

TITLE: Three-dimensional atlas of the macaque LGN

KEYWORDS: neurophysiology, macaque, rhesus monkey, lateral geniculate nucleus, brain atlas, visualization

AXIS I: 9 21

AXIS II: 77 84

INVEST1: E. Erwin

DEGREE1: BS

DEPT1: Physical Chemistry

NONHOST1:

INVEST2: J. Malpeli

DEGREE2: PhD

DEPT2: Psychology

NONHOST2:

% BRTP $: 12

ABSTRACT: We are constructing an atlas of the three-dimensional laminar structure and the mapping of retinal projections on the macaque lateral geniculate nucleus (LGN). Experimental data regarding the structure of the LGN obtained by J. Malpeli is embedded in a three-dimensional array. Large gaps in the data are being reconstructed by a semi-automatic process involving linear interpolation for the retinotopy and a model based on mean-field theory of Ising-spin systems for the laminar structure. The results will be included in a brain atlas database being created at the Lawrence Livermore National Laboratory, which will be made available to the public.

BRTP UNIT: C

TITLE: Mathematical models of LGN formation

KEYWORDS: morphogenesis, macaque, rhesus monkey, lateral geniculate nucleus, self-organizing maps, simulated annealing

AXIS I: 21

AXIS II: 41 77 84

INVEST1: E. Erwin
DEGREE1: BS
DEPT1: Physical Chemistry
NONHOST1:

INVEST2: J. Malpelli
DEGREE2: PhD
DEPT2: Psychology
NONHOST2:

INVEST3: S. Tzonev
DEGREE3: Diploma in Physics
DEPT3: Physics Department
NONHOST3:

INVEST4: D. Lee
DEGREE4: BS
DEPT4: Psychology
NONHOST4:

% BRTP $: 4

ABSTRACT: The lateral geniculate nucleus (LGN) relays nerve impulses from the retina to the visual cortex. The LGN of the macaque monkey contains six distinct cell laminae in certain regions, and four or two laminae in other regions. We are modelling the development of the macaque LGN during ontogeny with the aim of understanding why this morphology emerges. In particular, we are interested in why the transition between the six- and four-layered regions occurs at a position corresponding to the mapped boundary of the optic disk. Our approach to the problem utilizes several techniques including application of a modified self-organizing map algorithm and simulated annealing. We hope to elucidate general principles which will explain the differences in LGN morphology between species.

BRTP UNIT: T

TITLE: Biologically Plausible Neural Networks for Visuo-Motor Control

KEYWORDS: feature maps, information processing, movement, robotics

AXIS I: 9 21

AXIS II: 41 77 84

INVEST1: T. Hesselroth
DEGREE1: MS
DEPT1: Physics
NONHOST1:

INVEST2: K. Sarkar
DEGREE2: MS
DEPT2: Physics
NONHOST2:

INVEST3: K. R. Wallace
DEGREE3: B.Sc.
DEPT3: Physiology
NONHOST3: University of Oxford

INVEST4: P. P. van der Smagt
DEGREE4: MS
DEPT4: Computer Science
NONHOST4: University of Amsterdam

% BRTP $: 4

ABSTRACT: The ease with which the central nervous system performs motor control belies the computational complexity of the problem confronting it. This is particularly true for situations requiring movements of the hand to visual targets. We are investigating the information processing that the nervous system must perform to accomplish such tasks through the use of neural networks models of biological computation. These networks are based upon Kohonen's self-organizing feature maps and related algorithms formulated by members of our group. The research involves the development of computer models of both areas of the cerebral cortex associated with visuo-motor control, notably the visual system and association and sensorimotor

cortices, and sub-cortical areas such as the cerebellum. The aim is to develop models of these structures which can be interconnected in a hierarchical fashion similar to that found in humans and primates and which can operate concurrently. For the work we employ both computer simulations of limb movement and also a pneumatic robot arm to evaluate the performance of our models. We have successfully developed networks capable of controlling both these effectors and are now engaged in refining the biological fidelity of our existing networks and the inclusion of models of sub-cortical processing.

BRTP UNIT: T

TITLE: Dynamics of Coupled Neurons

KEYWORDS: excitable elements, Bonhoeffer-van der Pol-model, synchronous firing

AXIS I: 21

AXIS II: 77 84

INVEST1: C. Kurrer

DEGREE1: Dipl. Phys.

DEPT1: Physics

NONHOST1:

% BRTP $: 4

ABSTRACT: Experimental data has shown synchronous firing activity in neurons in the visual cortex of the cat codes similar features. This synchronicity is found to be dependent upon the stimuli in the visual field of the cat. Such observations suggest that synchronization may play a role as a coding principle for information being processed in the brain. We have previously proposed a mechanism for synchronous neural activity based on a dynamical description of single neurons as excitable elements with stochastic activity. For the work we employed the Bonhoeffer–van der Pol–model (BvP) to describe neurons. This model is a simplified version of the Hodgkin-Huxley equations which describe action potential propagation in nerve axons. Using this approach we have shown that weakly coupled neurons can develop synchronous firing patterns in response to variations in a parameter corresponding to the current input to the neurons. In terms of the nonlinear dynamics of the BvP model this parameter also controls the excitability of the system. Through the use of large scale simulations of coupled neurons and analytical investigations, we hope to elucidate mechanisms that govern the transition between asynchronous and synchronous dynamics. Our goal is to understand how synchronicity in the firing activity influences the overall dynamics and information processing capabilities of such networks of coupled neurons.

BRTP UNIT: C

TITLE: Diffusional Edge Enhancement in Nuclear Magnetic Resonance Microscopy

KEYWORDS: permeability, bounded diffusion, motional narrowing, Monte Carlo

AXIS I: 9

AXIS II: 63c 77

INVEST1: D. Barsky
DEGREE1: MS
DEPT1: Biophysics
NONHOST1:

INVEST2: B. Pütz
DEGREE2: MS
DEPT2: Physics
NONHOST2:

INVEST3: J. Schoeniger
DEGREE3: PhD
DEPT3:
NONHOST3: Sandia National Laboratory, Livermore, CA

INVEST4: E. Hsu
DEGREE4: MS
DEPT4: Radiology
NONHOST4: Johns Hopkins University, Baltimore, MD

INVEST5: S. Blackband
DEGREE5: PhD
DEPT5: Radiology
NONHOST5: Johns Hopkins University, Baltimore, MD

% BRTP $: 4

ABSTRACT: In NMR microscopy of liquid samples or tissues, the effect of molecular diffusion is usually to degrade resolution and sensitivity due to destructive interference of signals from the moving spins. Samples may contain, however, barriers impermeable to the translating spins. We have experimentally demonstrated that, in the presence of a magnetic field gradient, a reduction in the translational mean free path of liquid molecules, due to collisions with barriers, results in the enhancement of magnetization near these barriers. This edge enhancement is related to the previously predicted and numerically simulated effect of motional narrowing edge enhancement. Calculations, based on Monte Carlo simulations of diffusing and precessing spins, compare well with the experimentally observed results. This edge enhancement potentially provides a means to use NMR microscopy for visualizing small, impermeable structures that might otherwise be invisible. We are currently investigating the use of edge enhancement as a means of measuring the permeability of biological cells, such as red blood cells. In related work, we are employing Monte Carlo simulations to develop a coherent description of liposomal contrast agents, bringing together models based on susceptibility differences versus ones based on exchange.

	TECH RES & DEVEL (T)	COLLAB RES & SERVICE (C)	DISSEM & TRAINING (D)	TOTALS
NUMBER OF PUBLICATIONS	15	7	0	22
NUMBER OF SUBPROJECTS	7	8	0	15
NUMBER OF INVESTIGATORS	19	22	0	40[1]
PERCENT OF BRTP FUNDS ALLOCATED	44%	56%	0%	100%
SERVICE FEES COLLECTED	0	0	0	0
OTHER FUNDS ($)	58,000	42,000	–	100,000

[1]W. Humphrey is counted twice: once in the BRTP unit "T" and once in the BRTP unit "C".

State or Country	Number of Investigators
IL	31
IN	2
MA	1
MD	2
NC	1
CA	1
Netherlands	1
Israel	1

BRTP Unit C

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Barsky, Daniel	University of Illinois (Schulten, Klaus)	FED	NIH
Blackband, Stephan J.	Johns Hopkins University Hospital (Blackband, Stephan J.)	FED	NIH
Blasdel, Gary G.	Harvard Medical School (Blasdel, Gary G.)	FDN	
Erwin, Ed	University of Illinois (Schulten, Klaus)	FDN	
Feng, Zhou	University of Illinois (Schulten, Klaus)	FED	NIH
Freed, Karl	University of Chicago (Freed, Karl)	FED	NSF
Heller, Helmut	University of Illinois (Schulten, Klaus)	FED	NIH
Hermann, Robert B.	Eli Lilly Co. (Lilly Research Laboratories)	IND	
Hsu, Edward	Johns Hopkins University Hospital (Blackband, Stephan J.)	FED	NIH
Humphrey, William	University of Illinois (Schulten, Klaus)	SCCF	
Kostov, Konstantin	University of Chicago (Freed, Karl)	FED	NSF
Lee, D.	University of Illinois (Malpelli, Joseph)	FED	NIH
Logunov, Ilya	University of Illinois (Schulten, Klaus)	OTH	
Malpelli, Joseph	University of Illinois (Malpelli, Joseph)	FED	NIH

BRTP Unit C (cont.)

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Sheves, Mordechai	Weixmann Institute, Israel (Sheves, Mordechai)	OTH	
Obermayer, Klaus	University of Illinois (Schulten, Klaus)	FDN	
Pidgeon, Charles	Purdue University (Pidgeon, Charles)	IND	
Pütz, Benno	University of Illinois (Schulten, Klaus)	FDN	
Schoeniger, Joseph J.	Sandia National Laboratories (Schoeniger, Joseph J.)	FED	DOE
Tzonev, Svilen	University of Illinois (Schulten, Klaus)	FDN	
Chang, Xiao-Yan	University of Chicago (Freed, Karl)	FED	NSF
Xu, Dong	University of Illinois (Schulten, Klaus)	FED	NIH

BRTP Unit T

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Biesiadecki, Jeffrey	University of Illinois (Skeel, Robert)	FED	NIH
Bishop, Thomas	University of Illinois (Schulten, Klaus)	FED	NIH
Board, John A.	Duke University (Board, John A.)	FED	NSF
Heller, Helmut	University of Illinois (Schulten, Klaus)	FED	NIH
Hesselroth, Ted	University of Illinois (Schulten, Klaus)	FDN	
Humphrey, William	University of Illinois (Schulten, Klaus)	SCCF	
Kale, Laxmikant	University of Illinois (Kale, Laxmikant)	FED	NIH
Kufrin, Rick	University of Illinois (NCSA)	FED	NSF
Kurrer, Christian	University of Illinois (Schulten, Klaus)	FED	NIH
Kuszmaul, Chris	University of Illinois (Kale, Laxmikant)	FED	NIH
Leinkuhler, Benedict	University of Illinois (Skeel, Robert)	OTH	
Sarkar, Kakali	University of Illinois (Schulten, Klaus)	FDN	
Sinha, Amitabh	University of Illinois (Kale, Laxmikant)	FED	NSF
Skeel, Robert D.	University of Illinois (Skeel, Robert)	FED	NIH
Okunbor, Daniel I.	University of Illinois (Skeel, Robert)	FED	NIH

BRTP Unit T (cont.)

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
van der Smagt, Patrick	University of Amsterdam (Schulten, Klaus)	FDN	
Wallace, Ken	University of Illinois (Schulten, Klaus)	FED	NIH
Windemuth, Andreas	University of Illinois (Schulten, Klaus)	IND	
Zhang, Meiqing	University of Illinois (Skeel, Robert)	FED	NIH

BRTP unit: (T)

NUMBER PUBLISHED –

Books:	0	Papers:	8	Abstracts:	0

NUMBER IN PRESS –

Books:	0	Papers:	7	Abstracts:	0

Published:

In Press:

BRTP unit: (C)

NUMBER PUBLISHED –

Books:	0	Papers:	6	Abstracts:	1

NUMBER IN PRESS –

Books:	0	Papers:	0	Abstracts:	0

Published:

In Press:

BRTP unit: (D)

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

NUMBER IN PRESS –
Books: 0 Papers: 0 Abstracts: 0

Published:

In Press:

Advisory committee

An advisory committee has been recruited to meet the following needs of the resource: review success of main past projects and provide advice on new research, technological directions, collaborations, and community needs.

The following colleagues agreed to serve on this committee:

Chair: Christoph von der Malsburg, USC, Neurobiology, Max-Planck Institute for Brain Science, Frankfurt (Computational Neurobiology)

Bernie Alder, UC Berkeley, Physics (Computational Science)
Axel Bruenger, Yale, Biochemistry and Biophysics (Computational Biology)
Karl Hess, UIUC, Electrical Engineering (Computational Science)
Barry Honig, Columbia, Biochemistry (Computational Structural Biology)
Martin Karplus, Harvard, Chemistry (Computational Chemistry, Biology)
Paul Lauterbur, UIUC, Medical Information Science (Medical Imaging)

The first meeting of the advisory committee will take place in September 1993. The reorganization of the Resource in the initial phase of the first funding period, the late hire of the Resource Administrator and scheduling problems have thus far prevented a meeting of the committee occurring at an earlier date.

Dissemination and Training

The Resource currently employs several methods for dissemination of information and training.

In addition to the usual avenues of publication and invited lectures, we run a seminar series and print a series of Beckman Institute technical reports. Further, the Resource has access to 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). This past year a video was produced to highlight the research activities and goals of the Resource.

Source code and documentation for the two molecular dynamics packages developed within the Resource, EGO and MD, are available via anonymous ftp from lisboa.ks.uiuc.edu (128.174.214.14, directories /pub/md and /pub/EGO, respectively). Documentation and executable binaries for the program VRChem are also available from this ftp site (directory /pub/vrchem).

The Resource has provided training on the use of and accounts for access to the Transputer systems, as well as technical assistance in initializing a membrane-protein molecular dynamics study using EGO. The graphical display program VRChem has been installed for several researchers on and off campus.

Outside Lectures

The PI presented the following invited lectures:

- August 16–19, 1992, University of Minnesota, Minneapolis, Minnesota; International Workshop NNP2 (Neural Networks for Physicists #2): Lecture: *Brain Maps and the Geometry of Neural Computation: Theory, Observations and Applications.*
- September 23, 1992, Purdue University, West Lafayette, Indiana; Lecture: *Molecular Dynamics Simulations of Elementary Reactions in Membrane Proteins*
- October 8, 1992, University of Michigan, Lansing, Michigan; Lecture: *Molecular Dynamics Simulations of Elementary Reactions in Membrane Proteins*
- October 19, 1992, International Chemical Conference & Exhibition, Annecy, France; Lecture: *Use of Parallel Multi-processor Computers in Chemistry*
- November 6, 1992, The 44th Okazaki Conference, Okazaki, Japan; Lecture: *Elementary Reactions in Proteins*

- November 7, 1992, Hisaharu Hayashi Symposium, Tokyo, Japan; Lecture: *Micellar radical pair decay*
- November 19, 1992, Supercomputing '92, Minneapolis, Minnesota; Lecture: *Computational biology in the era of massively parallel machines*
- December 2–3, 1992, Symposium on Theoretical Biology, Heidelberg, Germany; Lecture: *Structure and Dynamics of Membrane and Membrane Proteins*
- December 10, 1992, NSF–DOE Institute in Computational Biology, Argonne National Laboratory, Argonne, Illinois; Lecture: *Molecular Dynamics Simulations on Massively Parallel Computers Algorithms, Hardware and Applications*
- January 12–13, 1993, Eli Lilly Company, Indianapolis, Indiana; Lecture: *Structure and dynamics of membrane and membrane-bound proteins.* Group: Eli Lilly personnel
- January 16–23, 1993, 28th Winter Seminar Klosters, Switzerland; Lecture: *Structure and Function of Membrane Proteins*
- March 6–8, 1993, Workshop on "High Performance Computing in Chemistry (HPCC)" Bethesda, Maryland; Lecture: *Simulating Biomolecular Assemblies*
- March 22–31, 1993, The Hebrew University of Jerusalem, "Workshop on Protein Dynamics and Thermodynamics," Jerusalem, Israel.
- April 8–11, 1993, NIH seminar, "Resource Management", Bethesda, MD.
- May 3–4, 1993, Symposium, "Simulation of Polypeptide and Protein Structure," Cornell Theory Center, Ithaca, New York; Lecture: *Large scale simulations of protein-membrane systems*
- May 10 – June 30, 1993, Fellow at the Institute for Advanced Studies, Hebrew University, Jerusalem, Israel.

The PI during the past year alsoseved on the following committees:

- NIH Special Study Section, San Diego, California, October 25-27, 1992
- NSF Super Computer Center Advisory Board;
- Beckman Institute Director Search Committee;
- Beckman Institute Program Advisory Committee;
- Computer Science Engineering Steering Committee, UIUC;

- National Research Council Committee on the Future of Computer Science

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

- SIGGRAPH '92, Chicago, Illinois (Humphrey, July 1992)
- SMRM 11th Annual Meeting, Berlin, Germany (Barsky and Pütz, August 1992)
- International Conference Computation of Differential Equations and Dynamical Systems, Beijing, China (Skeel, September 1992)
- Würzburg, Germany (Pütz, October 1992)
- 5th Annual Cell & Molecular Biology Molecular Biophysics Research Symposium, in the Beckman Institute, University of Illinois at Urbana–Champaign, Illinois (September 1992)
- International Conference on Scientific Computation and Differential Equations, Auckland, (Skeel, January 1993)
- DOE/OSC Applied Mathematics Workshop, Albuquerque, (Skeel, February 1993)
- 1993 ACM Symposium on Applied Computing, Indianapolis, (Board, February 1993)
- March Meeting of the American Physical Society, Seattle, WA, (Kurrer, March 1993)
- University of Kansas, Lawrence (Skeel, April 1993)
- Imperial College, London (Skeel, May 1993)
- London Mathematical Society Two Day Meeting, Numerical Analysis and Dynamical Systems, University of Cambridge (Skeel, May 1993)
- University of Southampton (Skeel, May 1993)
- Oxford University (Skeel, May 1993)

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. Günther Palm, Department of Neural Information Processing, University of Ulm, Germany, August 24, 1992. Lecture: *Neuronal Associative Memory with Local Learning Rules and Sparse Coding*
- Prof. Uli Nienhaus, Department of Physics, University of Illinois, Urbana, IL, September 28, 1992. Lecture: *Transitions in the Heme Pocket of Myoglobin*
- Prof. Annette Zippelius, Institut für Theoretische Physik der Universität Göttingen, Göttingen, Germany, October 12, 1992. Lecture: *Recognition and Categorization in a Structured Neural Network with Attractor Dynamics*
- Prof. Colin A. Wraight, Department of Physiology and Biophysics, Beckman Institute, University of Illinois, Urbana, IL, October 19, 1992. Lecture: *Electrostatic Interactions and Flash-Induced Proton Uptake in Reaction Centers From Rb. Sphaeroides*
- Prof. Eric Jakobsson, Dept. of Physiology and Biophysics/NCSA, Beckman Institute, University of Illinois, Urbana, IL, October 26, 1992. Lecture: *Computational Studies of Channels and Membranes*
- Prof. Carol Post, Dept. of Medicinal Chemistry, Purdue University, West Lafayette, Indiana, November 23, 1992. Lecture: *Flexible Active Sites Do Not Stabilize High-Energy Conformations*
- Prof. Charles Pidgeon, Department of Medicinal Chemistry, Purdue University, West Lafayette, Indiana,December 7, 1992. Lecture: *Antiviral Activity and Physical Chemical Studies of Heteroatom Phospholipids and Membranes*
- Ing. Rudi van Drunen, Dept. of Biophysical Chemistry, University of Groningen, The Netherlands, January 11, 1993. Lecture: *Gromacs: a software package and a parallel computer for molecular dynamics simulations*
- Dr. Andreas V. M. Herz, Physics of Computation Laboratory, Division of Chemistry, California Institute of Technology, January 25, 1993. Lecture: *Where Hebb and Lyapunov Meet: Unexpected Simplicity in Complex Systems with Delayed Feedback*
- Prof. David E. Goldberg, Dept. of General Engineering and Illinois Genetic Algorithm Laboratory, University of Illinois, Urbana, IL, February 1, 1993. Lecture: *A Wright-brothers Theory of Genetic-algorithm Flight*

- Prof. Axel T. Bruenger, Dept. of Biochemistry and Biophysics, Yale University Medical School, February 15, 1993. Lecture: *Studies of Helix-Helix Association in Soluble and Membrane Proteins*

- Dr. Bernard R. Brooks, Molecular Graphics and Simulation Laboratory, National Institutes of Health, Bethesda, MD, February 22, 1993. Lecture: *Using Molecular Dynamics and Distributed Architectures for Examining Temperature and Environmental Effects on Protein Dynamics*

- Chris Kay, Laboratory of Physical Chemistry, Oxford University, England, March 18, 1993. Lecture: *Elucidating Small Magnetic Field Effects*

- Stephen Batchelor, Laboratory of Physical Chemistry, Oxford University, England, March 18, 1993. Lecture: *Probing Radical Pair Processes*

- Dr. Ulrich Essmann, Center for Polymer Studies, Boston University, Boston, MA, March 19, 1993. Lecture: *Computer Simulation of Metastable Liquid Water*

- Christoph von der Malsburg, Institute for Neuroinformatics, Ruhr-University Bochum and Department of Computer Science, USC, Los Angeles, CA, March 29, 1993. Lecture: *Neural Networks with Dynamical Links*

- Dr. Qing Sheng, Laboratory of Atomic & Solid State Physics, Cornell University, Ithaca, NY, April 2, 1993. Lecture: *Looking for Quasicrystalline Minimal Surfaces*

- Dr. Tom Heskes, Department of Physics, University of Nijmegen, The Netherlands, April 5, 1993. Lecture: *Transition Times in Self-Organizing Maps*

- Dr. Klaus-Robert Müller, GMD First, Berlin, Germany, April 12, 1993. Lecture: *Sparsely Connected Hopfield Networks for the Recognition of Correlated Pattern Sets*

- Dr. Richard W. Pastor, Biophysics Laboratory, Center for Biologics Evaluation and Research, FDA, Bethesda, Maryland, April 26, 1993. Lecture: *Molecular and Stochastic Dynamics of Lipid Bilayers*

- Alex Ulitsky, Department of Chemistry, University of Illinois at Chicago, Chicago, IL, April 30, 1993. Lecture: *A Binary Collision Model as a Dynamic Correction to Mean Field Approximation*

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