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Annual Progress Report

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Principal Investigator:	
Klaus Schulten, PhD	

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Telephone Number:	(217) 244-2212
Facsimile Number:	(217) 244-6078
Electronic Mail Address:	kschulte@lisboa.ks.uiuc.edu

Summary of Research Progress

This progress report covers the fourth year, of an eight-year period of funding for the Resource. The year has been characterized by the acquisition of a major piece of equipment for parallel computing and by the formation of major collaborative efforts.

Twelve Hewlett-Packard 9000/735 workstations were delivered in December and were fully operational a couple of weeks later. In February and March components of an ATM switch from Fore Systems were delivered, and in one week the twelve workstations were functioning as a cluster of interconnected processors operating in parallel. Processor upgrades for these workstations have just arrived, but have not yet been installed. Also very important was the acquisition last summer and last fall of components of a 3D visualization facility: an Electrohome 4101-S large-screen stereo projector and a Polhemus Fastrak spatial tracking device for 3D pointing.

The past year has seen a widening scope of beneficial collaborations. On the technology side we are teamed with J. Board (Duke), A. Brunger (Yale), and T. Schlick (NYU) as part of an NSF Grand Challenge Application Group in the development and application of "Advanced Computational Approaches to Biomolecular Modelling and Structure Determination." We initiated our joint effort at a retreat in Pittsburgh in December and have a monthly teleconference to strengthen and enhance the collaboration. On the science side an award from the Carver Foundation for a project entitled "Bridging a gap between experimental and computational laboratories in structural biology" will enable vigorous interactions with experimentalists at Purdue, UC-Irvine, the Weizmann Institute in Israel, the Max Planck Society in Germany, and the University of Illinois. Also, we were awarded a large NSF Metacenter Resources Allocation of computing time on the CM-5 at the National Center for Supercomputing Applications, on the Cray C90 at the San Diego Supercomputing Center, and on the Cray C90 and T3D at the Pittsburgh Supercomputing Center.

The Resource advisory committee, consisting of B. Alder, K. Hess, B. Honig, M. Karplus, C. von der Marsburg, and A. Szabo, visited the resource on April 11 and a report was submitted to the NIH. On April 28 the Resource held an open house to present the facilities of the Resource to the UIUC campus.

This year marks a further shift toward structural biology in the scientific orientation of the Resource. Two students who have been working on MRI will be completing their work during the current period, and there will be a drop from six to two in the number of personnel working on neurobiology next year. Joining us for the next year will be a sizable number of new students and postdocs working in the area of structural biology. To train them, we are organizing a two-month "summer school," from which we will select the most promising students.

The remainder of this summary describes how the projects, presented in more detail in subsequent parts of the report, relate to the broader mission of the Resource.

Parallel Computing for Biology

In the past year the performance of high-end workstations based on commercial processor chips has continued to increase rapidly and fast ATM switches are expected to be marketed in large numbers. These developments have the effect of making customized parallel computers obsolete in short time, and they indicate that, in the near future at least, clusters of high performance workstations are expected to offer close to the best possible performance in a way that is very cost effective. Also, due to the maturation of the message-passing model of parallelism, as witnessed by the creation of the MPI standard, its power will become available to growing numbers of users. Workstations are not only much cheaper in price, but software is available that makes them useful for other, more routine tasks. Thus, it is anticipated that the workstation clusters will be a very popular option for research groups wanting high performance computing.

After a long and detailed study that compared machines from HP, IBM, SGI, and DEC, we chose to purchase workstations from Hewlett-Packard. A similar choice has been recently made by NCSA, which is purchasing from Convex their Exemplar system based on the use of HP workstation processors.

One of the principal activities of the Resource is development of new computer programs both for the computation and for the display of biomolecular dynamics simulations.

VMD is one of these tools designed to display molecular structures. It has been enhanced to take advantage of 3D pointing devices. Also, in the past year the program has been significantly improved so as to show the evolving frames in real time on a local graphics workstation while the simulation itself is being executed on a remote high performance computer, such as the CM-5 or our HP cluster. Future work will provide the ability to interact with the remote simulation.

In cooperation with a former Resource member (A. Windemuth) we have finished the first stage in the development of a new generation of molecular dynamics programs that possess scalable parallelism and calculate the full electrostatic interaction. The basis for this parallelism is spatial decomposition, in which the spatial domain is partitioned among the processors. This strategy combined with the use of the fast multipole algorithm gives a program which is nearly scalable in the sense that larger numbers of atoms can be simulated on proportionately larger numbers of processors with little net increase in computation time. Every other parallelization that we are aware of (with the exception of one in Daresbury, England) uses particle decomposition. We have now a first working

version of the program, not only for uniprocessors, but also for the CM-5 and the HP workstation cluster of the Resource.

Applications

The Resource has been pursuing several biologically important studies, which would be impractical without high performance computing:

1. Studies of membrane–drug and membrane–protein interactions.
2. Molecular dynamics study of the interaction of steroid hormone receptors with DNA response elements.
3. Studies of the development of cortical maps in the striate cortex and of multi-layered topographic representations in the lateral geniculate nucleus (LGN).
4. Studies of biologically plausible models of processes in the visuo-motor control.
5. Exploiting diffusional edge enhancement to measure membrane permeabilities.

Molecular Modeling on the Workstation Cluster

We have assembled hardware and software components of a system that we believe represents the most fruitful approach to the computer modeling of very large molecular systems.

We obtained at the end of 1993 a cluster of twelve Hewlett-Packard 735/99 workstations connected by an ATM switch from Fore Systems. These workstations are about to be upgraded with 125 MHz processors. This system delivers an excellent price/performance ratio. Presently, the HP-735 are the fastest workstations available. The ATM connections have a capacity of 100 megabits/sec and the switch has 16 ports which together can handle 2.4 gigabits/sec. Because of the general usefulness of workstations, we expect that this technology best represents the type of system likely to be used by researchers in computational biology, so we expect that parallel applications developed on this type of system will have widespread utility and impact.

The cluster is already heavily used by our collaborators and us. Parallel molecular dynamics applications, such as PMD, XPLOR, and EGO have been executed. Initial tests with the program PMD, developed at the Resource, indicate that a single HP running a serial version of PMD is as fast as PMD running in parallel on 32 nodes of the CM5 and that PMD on eight HP machines connected via ATM is faster than on 48 processors of the Intel Paragon. Further, an important component of our new molecular dynamics program, the fast multipole algorithm, improves its performance by a factor of 5 in going from one to eight HP processors. Tests with XPLOR on two molecular systems give speedups of 3.2 and 3.3 in going from one to four HP processors, and this performance is 61% of that of a Cray C90. Further performance improvements are expected with the installation of the upgraded processors.

PMD marks the beginning of a new generation of molecular dynamics programs designed to be computationally efficient for very large molecular systems, which is possible only on parallel and massively parallel computers. The program achieves parallelism through a partitioning of the spatial domain among processors. Complete calculation of the long-range electrostatics, which has been demonstrated to be very important in membrane applications, is achieved through the use of the fast multipole algorithm, developed in a collaboration with J. Board of Duke University. High efficiency is obtained through the use of separate timesteps for short- and long-range interactions. The program reads parameter sets from CHARM/XPLOR parameter files and coordinate files in standard format. Preliminary benchmarks with a system of 23,975 atoms on an ATM-connected cluster of eight HP-735 machines give a speedup of 5.8 compared to one machine and require a computing time of only 1.7 seconds per timestep.

We are further developing PMD. There are three important design criteria: (i) to be the

optimal program for doing the biomolecular investigations of the Resource and its collaborators, (ii) to facilitate experimentation with promising algorithms and computational techniques, and (iii) to exploit the availability of useful modules written by others, e.g., the fast multipole algorithm of J. Board and long-time integrators of T. Schlick. We have added features to PMD, partially documented the code, and, with J. Board, have developed a specification for program interfaces. We have ported the program to the CM-5 using its native message-passing library and to the HP-735 cluster using TCGMSG from Argonne. Performance in seconds of computing time per timestep for a system of 23,975 atoms is given below:

Number of Processors	Ethernet Runtime	Speedup	ATM Runtime	Speedup
1	10.9 secs	1.00	10.9 secs	1.00
2	6.9 secs	1.56	6.8 secs	1.60
4	5.0 secs	2.17	3.7 secs	2.92

These timings are for the first working version of the program, and we expect that the performance will improve greatly after improvements to the algorithms and coding.

Novel Graphic System for Molecular Visualization

In the past year, the Resource has developed a unique collaborative tool for visualization of molecular dynamics simulations. This system consists of a large-screen projection device integrated with a high-performance graphics workstation, and a spatial tracking device which provides a six-degrees-of-freedom pointer. The projector (an Electrohome 4101-S) is equipped with a special fast green-phosphor display tube, which allows it to display three-dimensional images that are easily viewed by several researchers simultaneously. The spatial tracking device (a Polhemus Fastrak) measures the position and orientation of several sensors relative to a fixed source, allowing a user to manipulate a three-dimensional pointer when viewing objects that are displayed in stereo. A final component of this system is the program VMD developed by researchers within the Resource, which takes maximal advantage of this equipment for visualization of biological molecules. This software also acts as a graphical front-end to the molecular dynamics programs MD and PMD developed within this Resource. In Figure 1, the use of this stereo projection facility for viewing biomolecular systems is illustrated.

Figure 1: Researchers discussing a stereo image of the glucocorticoid receptor DNA binding domain and corresponding DNA binding sequence.

There are several advantageous characteristics of this graphical display system:

- The large-screen projector allows several researchers to view the display simultaneously, benefitting collaborative projects.
- Images are shown in stereo, which dramatically improves the visual content of the displayed systems.
- A three-dimensional pointer helps alleviate one problem with three-dimensional images, that each person has a different viewpoint. The pointer provides a common reference point for each viewer.
- The projection and spatial tracking systems are relatively inexpensive ($20,000), and can be interfaced to a variety of graphics workstations.

The stereo projector and screen were installed during the summer of 1993, and the spatial tracking device was tested and installed in the fall of 1993. A Silicon Graphics 2-processor Onyx workstation, equipped with the VTX graphics option, continues to be the operating platform for this system. The projector echoes the display of the graphics workstation, and the spatial tracker is accessed via a serial port on the workstation.

The program VMD has been extensively modified to take advantage of these display and input devices, and serves as the primary application for displaying molecules in three dimensions. In addition to these display capabilities, VMD is designed to work with running molecular dynamics programs, to act as a graphical interface and to display a simulation being executed on a remote computer. In collaboration with Rick Kufrin of the National Center for Supercomputing Applications, VMD is being modified to allow it to initialize, control, and view the results of molecular dynamics simulations running on a variety of architectures. In the past year, the initial graphical interface and communication library have been completed, and the programs MD and PMD have been modified to work with VMD on Silicon Graphics workstations and on the Resource's Hewlett-Packard workstation cluster. This software is available via anonymous ftp from `ftp.ks.uiuc.edu`, including a 50-page User Guide [1].

This display system has proven to be an increasingly popular tool for the display and analysis of molecular dynamics simulations, and for presentations of ongoing projects in the Resource. Several groups at the University of Illinois, from the chemistry and biochemistry departments as well as groups within the Beckman Institute, have used this facility to view biological systems.

Studies of membrane–drug and membrane–protein interactions

Biological membranes are inherently related to very large heterogeneous environments and long-range molecular interactions. These systems show characteristic dynamic behavior over a broad range of time scales ranging from nanoseconds to seconds [2, 3] in processes such as lipid reorientation, lipid diffusion, solvation and transfer of drugs, and protein association. They play a fundamental role in living cells. The membrane environment is important for the reaction of many membrane proteins on the cell surface; it is also important in the process of drug transport. Obtaining structural models of membrane bilayers with atomic details is an important task for biophysicists to aid in the study of membrane–protein and membrane–drug interactions. Along with other research groups [4, 5, 6, 7], the Resource has been studying membrane models using molecular dynamics simulation techniques. The simulated membrane patches include 1-palmitoyl-2-oleoyl-*sn*-glycerol-3-phosphatidylcholine (POPC), dilauryl phosphotidylethanolamine (DLPE) membranes and recently Immobilized Artificial Membranes (IAM). The equilibrated membrane models have been used in studies of enzyme phospholipase A_2–membrane interactions and will be used in studies of drug transport across membrane bilayers.

Continuing on previous work dealing with the simulation of a POPC membrane bilayer [8], we have recently performed a simulation for a membrane bilayer consisting of 202 DLPE molecules and 8108 water molecules at 315 K [9]. The DLPE membrane has a different head group to that of the POPC membrane, which might play an important role in its interaction with phospholipase A_2 [10, 11]. We analyzed the structural properties of the new membrane, such as distribution functions of lipid groups, order parameters, and electron densities. However, the focus of the recent simulation has been placed on the analysis of the electrostatic properties of the membrane-water interface, such as the water polarization profile, the membrane dipole potential profile, and the susceptibility profile across the bilayer. These properties are important in the binding of peripheral membrane proteins and in the transport of small solute molecules. The quantities calculated from our simulation are in good agreement with available experimental data, which suggests that our model describes the electrostatic properties of the membrane reasonably well.

The equilibrated DLPE membrane patch has also been used in a study of phospholipase A_2–membrane interactions. Phospholipase A_2 is a well-known enzyme that has been purified and studied for more than a decade [12] with a well characterized 3-D structure [13, 14, 15]. The enzyme binds to membrane surfaces under suitable conditions and digests the lipid molecules by cleaving the *sn*-2 ester bond. Studies of this enzyme of the membrane-water interface are also motivated by the possible role of it in the inflammation processes [16]. We have simulated the enzyme on the membrane surface with a few different binding conformations. The properties of the enzyme–membrane complexes were compared for these different simulations and suggested that when phospholipase

A_2 is tightly bound to the membrane surface, partial desolvation of a few lipid head groups occurs. This desolvation may lead to the well-known activation of the enzyme on membrane surface [17, 18].

The membrane bilayers and membrane–protein complexes simulated typically consist of 30,000 atoms and require the calculation of long range forces for accurate simulation [9]. So far, the previous simulations were carried out using program MD on a single SGI or HP 735 workstation. We have recently started simulation with multiple processors on the HP workstation cluster using the program PMD. Using a 4 HP workstation in parallel, 15 ps long molecular-dynamics trajectories can be computed in one day. This has made nanosecond simulations an attainable goal for the Resource.

Another ongoing project is the simulation of Immobilized artificial membrane surfaces, in collaboration with Dr. Charles Pidgeon of Purdue University. IAMs are experimentally prepared by immobilizing synthetic single chain (or double chain) phospholipids on silica at monolayer density. These surfaces are useful for

- Predicting drug transport across biological barriers
- Purifying membrane proteins
- Catalyzing chemical reactions
- Reconstituting enzymes

We have recently started simulation of IAM surfaces to clarify their molecular properties with respect to natural fluid membrane surfaces. This computer analysis is intended to understand the molecular mechanisms for the observed phenomena that single chain immobilized phospholipids provide the same binding environment as non–bonded double chain phospholipid molecules that have assembled into fluid membranes. Preliminary simulations demonstrated that the immobilized membrane lipids form lipid clusters, a result which has been postulated from experimental NMR data. In addition, hydrogen bonding of the amide links was observed in the simulations which was suggested by experimental infrared data of the bonded phase. We will further equilibrate the IAM structure and compare the properties to previously simulated membranes and use these structures to study the incooperation of small drug compounds into IAM surfaces.

Molecular Dynamics Study of Steroid Hormone Receptors

The steroid hormone receptors are a closely related family of proteins that participate in the regulation of a wide variety of physiological and cellular functions in many species. The steroid hormones are responsible for regulating such basic physiological functions as metabolism, response to stresses, the reproductive system, growth and development. The mechanism by which the steroid hormones function is schematically represented in figure 2. The steroid binds the receptor, either in the cell cytoplasm or the cell nucleus, thus activating the receptor. The activated receptor binds to a specific sequence of DNA, typically as a dimer. These specific sequences of DNA are located some 100 to 1000 base pairs upstream from the target gene and the binding of the receptor to these sites on the DNA stimulates the synthesis of mRNA, eventually leading to an increase of a specific protein.

Figure 2: Schematic representation of the regulation of protein synthesis by steroids.

Various steps in this mechanism, hormone binding, DNA binding, and dimerization, can be mapped to independent functional domains of the receptors. The solution structure of the DNA binding domain (DBD) of several of these receptors has been determined by NMR. In addition to these solution structures, the crystallographic structure of the glucocorticoid receptor DNA binding domain(GR-DBD) bound as a dimer to DNA has been determined [19], and a similar structure corresponding to the estrogen receptor has been determined more recently [20]. The determination of these structures has given insight into the interactions necessary for the receptor to recognize a specific sequence of DNA.

We have conducted molecular dynamics simulations that compare the interaction of a GR-DBD dimer with a consensus DNA response element to the interaction of the same

GR-DBD dimer with a nonconsenus DNA response element. This system required the explicit inclusion of more than 3,000 water molecules in order to accurately reproduce physiological conditions. The resulting system contained nearly 14,000 atoms and therefore required the use of a parallel computer. The molecular dynamics simulations were performed using EGO, a program developed by members of the Resource for parallel computers. All simulations were run on the Parsytec GCel 64 node computer which was built by members of the Resource specifically for running parallel molecular dynamics programs.

These simulations indentified the protein-DNA interactions involved in the recognition of the DNA sequence by the GR-DBD. The results also identify several protein–DNA interactions which were not reported in the crystallographic analysis. These interactions agree with mutational experiments and homology data which indicate that specific amino acids are responsible for distinguishing between the various DNA response elements or that specific amino acids are needed to bind DNA. The molecular dynamics simulations also demonstrate that the protein will induce a bend of approximately 35° in the DNA, which was not observed in the crystallographic structure. However, gel-shift mobility assays indicate that members of this class of receptors do, in fact, bend their corresponding response elements by similar amounts.

The availability of crystallographic structures for two members of this class of proteins also offers us a unique opportunity to evaluate the success of computer modelling in predicting structures. In these computer experiments we are attempting to computationally mutate the structure of one known receptor into another known structure, in order to obtain the most successful protocol. Once the weaknesses and strengths of this method have been identified we will be able to predict with confidence the structures for the other members of this class of proteins, and thereby gain further insight into the nature of protein–DNA recognition.

Models of Lateral Geniculate Nucleus Development

Each hemisphere of the mammalian brain contains a distinct body called the lateral geniculate nucleus (LGN). Each nucleus 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 maps the opposite visual hemifield in a strict topographic fashion. Figure 3 illustrates a cross-section along the plane of symmetry of the LGN of the rhesus macaque monkey (*Macaca mullata*) provided by J. Malpeli, an experimental neurobiologist at the University of Illinois. Resource staff are currently pursuing a number of theoretical investigations into the structure and function of the LGN in a close collaboration with Dr. Malpeli and his research group.

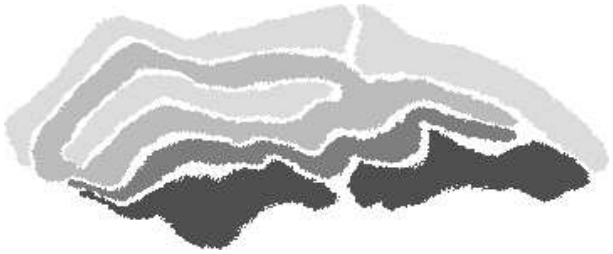

Figure 3: A slice of the macaque LGN viewed in a cross section along its plane of symmetry. The different shades code for morphologically and functionally different types of cells. Cells in one layer receive input from one eye only and have the same type of responces but different from those of cells of other layers. Representations of a point in the visual field are found in all layers and lie in a narrow column perpendicular to the layers. Note the gaps in some of the layers and the two distinct laminar patterns at both sides of these gaps. Data from the research group of J. Malpeli.

Only morphological data for the layers of neurons is shown in Figure 3. Dr. Malpeli has also obtained data on the topographic mapping of the retinas in each layer using *in vivo* micro-electrode recording techniques [21]. These data, though incomplete, provide the most detailed description available of the LGN of any species. The form of the layers and the embedded topographic maps have only been reconstructed along certain cross-sections along three sets of mutually perpendicular axes. Based on these experimental data, we have completed a three dimensional reconstruction of the morphological organization of the LGN. Currently we are working on a reconstruction of the retinotopic maps in the LGN. A full three-dimensional atlas of the rhesus monkey LGN will then be completed and made available in a database at the Lawrence Livermore National Laboratory. These three-dimensional reconstructions are also being utilized by Resource members who are modelling the LGN formation.

In collaboration with J. Malpeli's lab we are studying the development of the LGN morphology based on the most relevant principles of neural tissue growth and development.

In one approach the structure formation is simulated by an annealing technique in a two-dimensional model. Results of this approach capture some of the general features of the observed data. For example, in most simulations the presence of the optic disc forces the transition between a six- and a four-layer region to occur at the position of the optic disc gaps in the retinotopic map [22].

A more ambitious and more realistic approach developed by members of the Resource is a three-dimensional dynamic model of LGN formation. The model describes the gradual emergence of the laminar structure and neuronal functional properties as a process of competition between retinal ganglion cells for establishing permanent synapses on the LGN cells. Local cell interactions combined with strict retinotopy propagate an initially localized laminar pattern. In this model a wave of development sweeps through the initially homogeneous LGN, a fact which is consistent with experimental observations [23]. The model produces realistic laminar patterns and predicts causal relationship between the location of the transition between the two patterns and the blind spot gaps as shown in Figure 3. As found in the simulated annealing model, sufficient perturbation in the retinotopic map can trigger a transition in the laminar pattern. We have implemented a serial version of the model on a single workstation of our HP cluster. Further development, including simulations of larger systems and more detailed modeling of the establishment of the topographic maps in the LGN, will require use of several nodes running in parallel.

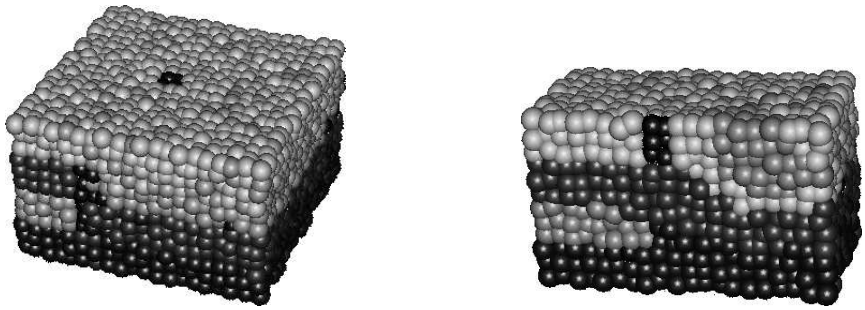

Figure 4: Left: mature state of the macaque LGN — result of the dynamic model. The different shades of the spheres code for cells with different functional properties. Only the parvocellular (upper four) layers are shown in this picture. Gaps in the uppermost (first) and third layers (gap not visible) are coded by the darkest color and coincide with the transition line between 4- and 2-layered patterns. Right: a cut of the three-dimensional structure along its plane of symmetry. Compare with the upper layers in Figure 3. Spatial segregation between layers is not modeled explicitly.

The dynamic model makes predictions which can be checked by experiments on the developing macaque LGN. Among them is a prediction of a particular shape of the wave front of the developmental wave — the rate of cell development must be anisotropic and fastest along the horizontal meridian. The proposed model can also account for patterns observed in other primates, e.g., in human and old-world monkeys. Using the macaque LGN as a model system we hope to better understand the general rules of structural

development of a class of brain structures and even of brain units in general.

Modelling Biological Visuo-Motor Coordination

The ease with which the central nervous system performs visuo-motor control belies the computational complexity of the problem confronting it. This is particularly true for situations requiring movement of the hand to visual targets. This type of hand-to-eye coordination is of prime importance for higher biological systems such as primates, as may be witnessed by our own manipulative capabilities. Furthermore, the motor capabilities of biological systems currently far exceed those of any artificial movement system. Hence, there is considerable interest in the question of how the strategies developed for controlling movement by biological systems may be adapted to solve problems associated with the control of movement of these latter systems.

The research effort of the Resource into this issue began several years ago with the publication of a paper discussing a neural network model based upon the self organizing feature map algorithm, originally proposed by Kohonen, [24] that was capable of learning the control of a simulated robot arm [25]. One motivation for such an approach is the well-known somatotopic organization of motor areas of the cerebral cortex which may be formally represented as a two-dimensional Kohonen network. In such formal networks each neuron within the network is assumed to correspond to a cortical column which constitutes the fundamental operational unit of the sensorimotor cortex.

In pursuing this type of research several different approaches to the problem have been investigated. Much of the early research activity concentrated upon the development of applications of such networks [26] to the problem of controlling either simulations of, or actual robotic systems. The emphasis in these studies was upon defining the information processing steps necessary to achieve accurate visuo-motor control in an abstract manner. In doing so quantitative measures of the performance of several neural networks algorithms when controlling movement were established. These results led to the Resource acquiring a SoftArm robotic manipulator to act as a test-bed for algorithms being developed by members of the group. Movement of this robot is controlled by muscle-like actuators driven by compressed air, and consequently is both compliant and hysteretic, two characteristics of movement shared by the SoftArm and the human arm. As such, effective control of this system presents a more difficult, but realistic, approximation of the problems confronting the nervous system when controlling movement of a limb such as the arm. Nonetheless, accurate positioning of this system was achieved using the formal algorithms developed by members of the Resource [27], thereby providing a practical demonstration of the utility of the networks.

More recently a second approach to issues of visuo-motor control has been developed to augment these established techniques. This effort is focussed on the development of neural architectures which are modelled directly on areas of the central nervous system associated with movement. This has led to the development of a network model of the primate

posterior parietal, motor and sensory cortices, ventralateral thalamus and cerebellar nuclei that learns to control the movement of a simulated planar arm through associations between different sensory modalities. During reaching movements to visual targets input to a set of motor cortex efferent zones arising from these elements determines the motor signals sent to the simulated limb. Long-term potentiation (LTP) occurring within the motor cortex, gated by input from the sensory cortex, facilitates the learning of novel movements in a manner similar to that observed in primates during the acquisition of motor skills. The model provides a framework for understanding motor cortex-cerebellar interactions during learning of movement that accounts for experimental observations regarding the importance of sensory cortex input to the motor cortex and the relationship between the firing rate of motor cortex cells and the orientation of the hand in the workspace during movement.

This work is now being extended to include consideration of the interactions and processing necessary to allow multiple motor cortex efferent zones to jointly control movement of both a simulated limb and the SoftArm manipulator within three-dimensional space. In addition, further quantitative investigations to establish more precisely the extent to which the acquisition of novel motor skills may be determined by the type of model we have proposed are being undertaken.

Developing NMR microscopy for tissue characterization

In NMR microscopy of liquid samples or tissues, the effect of molecular diffusion is usually to degrade resolution and sensitivity due to incoherent interference of signals from the moving spins. Most analyses of diffusion in NMR microscopy, however, have assumed that the diffusion coefficient does not vary within the sample. In the regions being imaged there may exist areas that differ markedly in the translational diffusion coefficient of the molecules whose magnetic resonance is being measured, and in particular, samples may contain barriers impermeable to the translating spins. In collaboration with J. Schoeniger (Sandia National Laboratory), E. Hsu, and S. Blackband (both Johns Hopkins University), 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 an enhancement of magnetization near these barriers. This edge enhancement is related to the previously predicted and numerically simulated effect of motional narrowing edge enhancement [28, 29]. We have reported systematic experimental observations of diffusional edge enhancement in one- and two-dimensional Fourier encoded NMR microscopy as well as results from Monte Carlo simulations of diffusing and precessing spins [30]. The numerically intensive simulations were performed on networks of workstations available on-site at the Resource. This allowed us to study different experimental setups and parameter variations in an almost interactive manner and provided valuable insights in the microscopic processes giving rise to edge enhancement, information not accessible through experiments.

Figure 5 (a) shows the magnetization profile after diffusion weighting and Fourier encoding along a direction perpendicular to a water-filled capillary. The edge enhancement appears as two prominent peaks. In an observed 2DFT image, Fig. 5 (b), two sickle-shaped maxima are clearly visible at the boundaries along the diffusion-weighting axis (almost horizontal in image) while no distortion can be seen in the orthogonal direction. This effect may provide a means for detecting boundaries in NMR micrographs, even when the actual boundaries themselves cannot be resolved.

Although biological cells are usually too small to be resolved by current NMR microscopy techniques, the cumulative effect of membrane-induced edge enhancement by many cells can yield information related to the average permeability of cell membranes. In further collaboration with Schoeniger and Blackband, we have exploited this cumulative effect in diffusion-weighting experiments to measure the permeability of red blood cell membranes (prepared as ghosts), obtaining a permeability P_d of 2×10^{-3} cm/s, a factor 1.5 to 2 times lower than what has been obtained by NMR using contrast agents [31]. These results can be compared with those obtained by Tanner [32] who used a similar method to ours but found values more than a factor 3 larger than the values obtained by NMR using contrast agents. We have demonstrated, through solutions of the diffusion-Bloch

Figure 5: NMR microscopy of a 600 μm water-filled glass capillary. (a) Observed (solid) and simulated (dotted) magnetization profile by Fourier transform of the FID signal. (b) Observed 2DFT reconstruction.

Figure 6: Magnetization versus position along the diffusion-weighting axis. The plots for $P_d = 0$ and $P_d = 1.4 \times 10^{-3}$ cm/s are almost identical. By measuring the area underneath the curves we find that roughly 43% of the magnetization is preserved *outside* the cell. The magnetization is expressed as a fraction of the initial value. The jaggedness of the plot is caused by the polygonal approximation of a circular cell in the finite-lattice solution of the diffusion-Bloch equations.

equations, that the geometrical configuration of the cells in the tissue, including their shape and connectivity, can greatly affect these methods of measuring cell permeability. In Fig. 6 we present a magnetization profile for a single red blood cell in the center of a 150 μm capillary. Clearly the magnetization preserved depends on the permeability of the membranes and the size of the cell. Since there is substantial magnetization preserved outside the cell, the shape and arrangement of cells greatly affects the signal remaining.

We are working towards a model which incorporates these factors into the derivation of membrane permeabilities by this diffusion-weighting method.

BRTP UNIT: T

TITLE: HP Cluster

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AXIS I: 9 11

AXIS II: 42 70 74

INVEST1: Ken Wallace
DEGREE1: D.Phil.
DEPT1: Beckman Institute
NONHOST1:

INVEST2: William Humphrey
DEGREE2: MS
DEPT2: Physics
NONHOST2:

INVEST3: Amitabh Sinha
DEGREE3: BS
DEPT3: Computer Science
NONHOST3:

INVEST4: Svilen Tzonev
DEGREE4: MS
DEPT4: Physics
NONHOST4:

% BRTP $: 20

ABSTRACT: In the beginning of 1994 the Resource obtained a cluster of twelve Hewlett-Packard 735/99 workstations connected by an ATM switch from Fore Systems. The HP workstation cluster and ATM represents the technology that is most promising in parallel computing, because it provides one of the best price/performance ratios available in current day parallel computers. It also represents technology that is widely available to researchers in computational biology. Therefore, we expect that applications developed for this technology will have widespread utility and impact.

The cluster is already being heavily used both by our collaborators and members of the Resource. We have run parallel molecular dynamics applications, such as PMD, XPLOR, and EGO, in addition to sequential applications, such as MD and

XPLOR. The HP workstations in the cluster are proving very valuable in running MD programs on individual processors. Many researchers in and outside the group tend to run MD programs on one processor at a time. The PMD program on one HP workstation performs better than on 32 processors of the CM-5. The cluster has been used in parallel mode also. Our current tests on PMD indicate that PMD runs faster on 8 HP workstations than on 48 processors of the Intel Paragon. Tests with the program EGO indicate that EGO runs as fast on 5 HP workstations as it does on 32 processors of the CM-5. Further, an important component of our new molecular dynamics program, the FMA algorithm, speeds up by simulations by a factor of 5 on 8 HP processors. Although a decrease in utilization is expected with parallelization, clearly the speedups are substantially lower than the number of processors at this point, and it suggests a need for further research on load balancing and other factors responsible for the performance loss.

BRTP UNIT: T

TITLE: Molecular Dynamics Programs

KEYWORDS: scalable parallelism, message passing, fast multipole algorithm

AXIS I: 9

AXIS II: 42 84

INVEST1: Robert Skeel
DEGREE1: PhD
DEPT1: Computer Science
NONHOST1:

INVEST2: Laxmikant Kale
DEGREE2: PhD
DEPT2: Computer Science
NONHOST2:

INVEST3: Amitabh Sinha
DEGREE3: BS
DEPT3: Computer Science
NONHOST3:

INVEST4: Mark Nelson
DEGREE4: BS
DEPT4: Computer Science
NONHOST4:

INVEST5: Joel Shi
DEGREE5: MS
DEPT5: Beckman Institute
NONHOST5:

% BRTP $: 10

ABSTRACT: Two parallel programs have been developed at the Resource: EGO, written in Occam by H. Heller for a Transputer machine, and PMD written in C by A. Windemuth for distributed memory machines. Only PMD will be further developed significantly. EGO will be maintained as a check on the accuracy and performance of PMD.

EGO has been translated to C and to Charm, which is an extension of C that we have developed for parallel programming. C-EGO and Charm-EGO have different parallel control modules: C-EGO supports the synchronous message passing of Occam, while Charm-EGO uses the asynchronous and message-driven execution model of Charm. Further, Charm-EGO performs the calculation of the electrostatic and the bonded forces concurrently, while C-EGO does them sequentially. We have verified the accuracy of Charm-EGO for a few sample molecular structures. It runs on a variety of parallel machines—clusters of workstations, CM-5, Intel Paragon, NCUBE-II, and Encore Multimax. For the CM5, we have obtained a speedup of 1.9 in going from 32 to 64 processors and a speedup of 3.5 in going from 32 to 128 processors. With better load balancing, we expect to obtain significantly better performance.

The other program, PMD, employs parallelism that is nearly scalable in computation time, memory, and communication time. The parallelism is based on partitioning the spatial domain among processors and the use of the fast multipole algorithm. The latter was implemented in a collaboration with J. Board. After Windemuth left the Resource, we have continued to collaborate with him. Also, we started developing our own version of PMD, which we call PMDi. We have begun documenting PMDi and have added some features: a restart capability to periodically save the current state of the computation, the ability to generate files suitable for use with VMD and Quanta, and an option for harmonic boundaries. We have ported the program to the CM-5 using its native message-passing library and to the HP cluster using TCGMSG from Argonne. For the CM-5, we worked on vectorizing PMD using C*. In order to determine the potential performance gains from vectorization, we wrote an optimized program for Lennard-Jones interactions, and obtained performance as high as 9 Mflops per node.

Progress has been made on development of new algorithms including symplectic multiple timestepping, smooth switching functions for cutoffs, efficient "SHAKE dynamics," flexible torsion dynamics, and long-time integration via normal mode analysis.

BRTP UNIT: D

TITLE: Interactive Molecular Visualization and Dynamics

KEYWORDS: molecular graphics, interactive simulation

AXIS I: 2 9 11

AXIS II: 42 70 74

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

INVEST2: Rick Kufrin
DEGREE2: BS
DEPT2: National Center for Supercomputing Applications
NONHOST2:

INVEST3: Andrew Dalke
DEGREE3: MS
DEPT3: Physics
NONHOST3:

% BRTP $: 16

ABSTRACT: We have been developing a molecular graphics program, VMD, which is a collaborative visualization tool that allows users to interact with and alter a running molecular dynamics simulation. An Electrohome ECP 4101-S projector equipped with a fast green-phosphor display tube which can display a large (6 by 8 feet) picture has been installed. The graphics is produced by the program VMD running on a 2-processor Silicon Graphics Onyx. With this arrangement ten or more people, wearing stereo glasses, can view and discuss biomolecular structures. VMD is also a front end for the molecular dynamics program PMD, developed at the Resource. This allows one to set up a simulation using VMD, run the simulation using PMD, and view the results with VMD while the simulation is executing. We have been working on a means to facilitate interaction with the stereo image. For this purpose, a Polhemus Fastrak tracker is used to get spatial and orientational information from two sensors. We have developed several visual tools for VMD that use this data. One behaves like a 3D pointer as it can be used to point to features in the image. Other tools control the eye position or move and reorient the molecule. We are working on the ability to structurally alter a molecular system with the pointers by coupling the graphics to a running simulation.

BRTP UNIT: C

TITLE: Molecular Modeling of Artificial Membranes

KEYWORDS: IAM, membrane structure

AXIS I: 6 9

AXIS II: 74f,h

INVEST1: Qing Sheng
DEGREE1: PhD
DEPT1: Beckman Institute
NONHOST1:

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

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

% BRTP $: 12

ABSTRACT: A 200 ps molecular dynamics simulation of a membrane bilayer, consisting of 202 dilauryl phosphatidylethanolamine (DLPE) molecules and 8108 water molecules at 315 K, has been conducted. Distribution functions of lipid groups, order parameters and other properties of the lipid bilayer were calculated and compared with experimental measurements. A detailed analysis was conducted for the structure of the membrane–water interface. The water polarization profile, the membrane dipole potential profile, and the susceptibility profile were calculated. Simulation results suggest that the polarization of water is determined mainly by the distribution of lipid head groups in the interfacial region. The membrane dipole potential is mainly due to the ester groups linked to the glycerol backbone. The susceptibility profile suggests a dielectric constant around 30 for the head group–water interface, and a dielectric constant around 10 for the ester group region. The ammonium groups of the DLPE membrane were found to form hydrogen bonds with water molecules, while no orientational preference was observed for water molecules

around the choline groups of a previously simulated POPC membrane. Correlations of the membrane surface charge density were also analyzed. The simulations which involved 32,808 atoms included Coulomb forces between all atoms evaluated by means of the Fast Multiple Algorithm. The calculation was carried out using the program MD on single SGI and HP 735 workstations.

We have also constructed a patch of IAM (immobilized artificial membrane) consisting of 36 phosphatidylcholine (PC) lipid molecules end-grafted on a 6×6 square lattice with the distance between PC being 8.5 Å(this value is taken from experimentally measured surface area per lipid molecule). The lateral dimensions of the monolayer are 51 Å×51 Å. A water layer 23 Å thick (1340 water molecules) was used to solvate the head group region. The whole system consists of 7815 atoms. To reduce the boundary effect, a two–dimensional periodic boundary condition was used. The boundaries in the third dimension, i.e., the normal direction of the membrane patch, were taken care of in two ways: the hydrocarbon tail end of each PC molecule was fixed to a lattice point and the oxygen atom of each water molecule within 3 Å from the boundary was also fixed to its initial location. In order to correctly represent the thickness of the membrane, 10 ps of the molecular dynamics at 300 °K was carried out before we fixed the boundary on the water side. The simulations are being performed using the program XPLOR on the HP cluster. This project is a collaborative effort with C. Pidgeon of Purdue University.

BRTP UNIT: C

TITLE: Molecular Dynamics Study of Bacteriorhodopsin Pump Cyle

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

AXIS I: 2 6 7A

AXIS II: 74h

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

INVEST2: Ilya Logunov
DEGREE2: MS
DEPT2: Chemistry
NONHOST2:

INVEST3: Dong Xu
DEGREE3: MS
DEPT3: Physics
NONHOST3:

INVEST4: Mordechai Sheves
DEGREE4: PhD
DEPT4: Organic Chemistry
NONHOST4: Weizmann Institute, Israel

% BRTP $: 8

ABSTRACT: Bacteriorhodopsin (bR), a protein found in the cell membrane of Halobacterium halobium, functions as a light-driven proton pump which drives ATP synthesis. A retinal chromophore bound via a Schiff base linkage to Lys-216 participates with the protein in a cyclic process which transfers a proton from the cytoplasmic to the extracellular side of the membrane. The retinal isomer composition in bR is 66% 13-*cis* and 34% all-*trans* in the dark-adapted form of the pigment (DA). Retinal in the bR_{568} pigment exists in the all-*trans*,15-*anti* configuration, and in the bR_{548} pigment in the 13-*cis*,15-*syn* configuration. We have studied structures and photocycles of both bR_{568} and bR_{548} by means of molecular dynamics simulations. All simulations

used the same parameters, and were done on SGI and HP workstations operated by the Resource.

The structure of bR_{568}, as provided by the so-called Henderson model [33], has been refined using molecular dynamics simulations [34]. The refined structure is characterized in view of bacteriorhodopsin's function. The key feature is a retinal Schiff base counterion complex which is formed by a hydrogen bridge network involving six water molecules and which exhibits Schiff base nitrogen of 6 Å and 4.6 Å.

Starting from a refined structure of bacteriorhodopsin with added inter-helical loops and sixteen water molecules in the L intermediate of the bR_{568} pump cycle, we transferred a proton from the protonated Schiff base to Asp-85 and employed a simulated annealing schedule to generate the long-lived M intermediate. The simulations resulted in very heterogeneous M intermediates, comprising a sequence of conformations which correspond to switching the Schiff base from hydrogen bonding contact with the extracellular site to hydrogen bonding contact with the cytoplasmic site of the protein.

Simulations of the bR_{548} photocycle resulted in structures consistent with the J, K, and L intermediates experimentally observed in the photocycle of bR_{548}. The results offer an explanation why an unprotonated retinal Schiff base intermediate, i.e., an M state, is not formed in the bR_{548} photocycle. The simulations suggest also that leakage from the bR_{548} to the bR_{568} cycle arises due to an initial 13-*cis*,15-*anti* $\rightarrow$ all-*trans*,15-*anti* "bicycle peddle" photoisomerization.

BRTP UNIT: T

TITLE: Molecular Dynamics Study of a Sequence Specific Protein-DNA Interaction

KEYWORDS: molecular dynamics, DNA, protein-DNA interaction, nuclear receptor hormone

AXIS I: 9

AXIS II: 74e,g,h

INVEST1: Tom Bishop
DEGREE1: MS
DEPT1: Chemistry
NONHOST1:

% BRTP $: 6

ABSTRACT: The crystal structure of the DNA-binding domain(DBD) of the glucocorticoid receptor (GR) complexed with DNA [19] has been used as a reference structure in order to create protein–DNA systems for investigation with molecular dynamics simulations. The crystallographic structure contained the coordinates for the GR-DBD dimer complexed with a non-consensus glucocorticoid response element (GRE). These coordinates were modified to restore the GRE to a consensus response element and to create a GR-DBD dimer complexed with a consensus GRE. The two resulting protein–DNA systems, corresponding to a consensus and nonconsensus response element, were each encapsulated in an ellipsoid of water, the larger system containing over 3,000 water molecules and totaling 13,500 atoms for the complete system. Two other systems were created as experimental controls. One system contained only the consensus response element encapsulated in an ellipsoid of water and the other system contained one of the GR-DBD monomers encapsulated in an ellipsoid of water. The dimensions of the enclosing ellipsoids for the protein–DNA systems were approximately 60 Å × 60 Å × 80 Å. Smaller ellipsoids were used for the control systems. Each protein–DNA system was simulated for 90 ps and each of the control systems was simulated for 45 ps. A harmonic boundary was enforced for the duration of each simulation, so that all water molecules were restricted to an ellipsoidal region of space slightly larger than the original dimensions used to create the water capsules. No further constraints were applied during the simulations. The molecular dynamics simulations were conducted using EGO, a program developed by members of the resource specifically for parallel computers. All simulations were run on the Parsytec GCel 64 node computer which utilizes Inmos T805 processors. The results of the simulations indicate that the GR-DBD dimer complexed with a

consensus response element has achieved a greater degree of protein–DNA interaction than the GR-DBD dimer complexed with a nonconsensus response element, and several protein–DNA interactions have been identified which were not previously reported in the crystallographic analysis.The simulations further indicate that the DNA is distorted by the protein–DNA interactions resulting in a localized bend of approximately 35°. The bend was not observed in the crystallographic structure; however, our results agree well with results from gel-assay experiments conducted on the estrogen receptor DNA binding domain.

BRTP UNIT: C

TITLE: Modelling the Morphogenesis of the Rhesus Lateral Geniculate Nucleus

KEYWORDS: macaque monkey, development, pattern formation, layers, thalamus

AXIS I: 1d 21 25b

AXIS II: 41 60 77

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

INVEST2: Ed Erwin
DEGREE2: BS
DEPT2: Chemical Physics
NONHOST2:

INVEST3: Joseph Malpeli
DEGREE3: PhD
DEPT3: Psychology
NONHOST3:

% BRTP $: 8

ABSTRACT: In the rhesus LGN, cells are sorted by type into 6, 4, or 2 distinct layers, depending on the visual-field eccentricity. The transition from 6 to 4 layers always coincides with small laminar gaps representing the blind spot. We have developed a 3-D model in which formation and segregation of initially unspecified geniculate receptive fields is driven by local cell interactions. Combined with strict retinotopy, these interactions propagate a 6-layered pattern (initially localized to the posterior, foveal pole) in a wave of development that sweeps through the LGN. Although a 4-layered pattern is more stable than the initial pattern, without a blind spot the 6-layered pattern tends to be propagated by local interactions to the anterior pole. However, with a blind spot, when the developmental wave reaches the gaps, the disruption of strict retinotopy triggers a transition to 4 layers.

Final laminar structure is determined by several factors, including initial pattern established at the posterior pole, cell interaction distances, and the size and location of the blind spot gaps. The shape of the developmental wave front plays a crucial role: realistic transitions are obtained only when the speed of the wave is

anisotropic (fastest along the horizontal meridian). The model is general enough so it is possible to be extended to other primate (including human) geniculate patterns. It is possible that structural singularities play a similar role in the morphogenesis of other biological structures.

BRTP UNIT: C

TITLE: Models of Pattern Development in the Macaque Visual Cortex

KEYWORDS: visual cortex, striate cortex, orientation preference, ocular dominance, macaque monkey

AXIS I: 25B 21

AXIS II: 77 41 60 63

INVEST1: Ed Erwin
DEGREE1: BS
DEPT1: Chemical Physics
NONHOST1:

INVEST2: Klaus Obermayer
DEGREE2: PhD
DEPT2: Physics
NONHOST2: University of Bielefeld, Germany

% BRTP $: 6

ABSTRACT: The primary visual cortex is segregated into regions such that visual features with different properties are processed at different locations in a functional map. These visual maps have been widely studied as a testing ground for general theories of cortical development, since it is relatively easy to study the effects on the patterns of changes in an animal's early visual environment. A large number of models have been proposed which attempt to explain either the structure or the formation of these visual maps.

The recently developed technique of optical imaging has allowed the patterns of visual orientation and ocular dominance maps to be revealed in greater detail than had been previously available. We undertook a comparison of the predictions of a variety of prominent models of visual map development. We analyzed the data from the imaging experiments. We noted many qualitative and quantitative constants of the map patterns, some revealed for the first time.

Computational models were implemented in computer programs. Their predictions were compared against one another and against the experimental data. It was found that even for models which appeared to have very different foundations, there were specific common principles which underlay most modelling approaches. These common fundamental principles caused the models to make similar predictions. However, we also discovered some differences between the individual model

predictions. These differences allowed us to exclude several models from consideration as valid models of visual map pattern formation. However, for most models, discrepancies between model predictions and experimental results can probably be eliminated by attention to the principles outlined by our research.

BRTP UNIT: T

TITLE: A Model for the Functional Development of the Primary Visual Cortex

KEYWORDS: primary visual cortex, V1, lateral geniculate nucleus, receptive field, inhibition, feature map, orientational selectivity, image processing

AXIS I: 9 21

AXIS II: 41 77 84

INVEST1: Ted Hesselroth

DEGREE1: MS

DEPT1: Physics

NONHOST1:

% BRTP $: 4

ABSTRACT: The development of the image processing capabilities of the primary visual cortex is studied via computer simulations. A neural network model has been formulated which includes the retina, the lateral geniculate nucleus, and the primary visual cortex. Of particular interest is the acquisition of orientational selectivity by cortical neurons and the organization of neurons within the cortical layer. We have shown that various physiological properties of the visual system may be explained by a plausible learning mechanism. Additionally, the dynamics of neural activities are being studied by applying the fully-formed network to real images, and we are presently investigating how other observed visual properties may arise from such neuronal dynamics.

BRTP UNIT: T

TITLE: Modelling Cortical Processing During Visuo-Motor Control

KEYWORDS: motor control, information processing, movement, robotics

AXIS I: 9 21

AXIS II: 41 77 84

INVEST1: Ken Wallace

DEGREE1: D.Phil.

DEPT1: Beckman Institute

NONHOST1:

% BRTP $: 4

ABSTRACT: We have developed a network model of several areas of the nervous system associated with motor control that learns to control a simulated planar arm through associations between different sensory modalities. During reaching movements to visual targets input to a set of motor cortex efferent zones is provided by projections arising from associative areas of the cerebral cortex, thalamic input originating as output from the cerebellum and cortical projections from the sensory cortex. Long-term potentiation (LTP) occurring within the motor cortex, gated by input from the sensory cortex, facilitates the learning of novel movements in a manner similar to that observed in primates during the acquisition of motor skills. The model provides a framework for understanding motor cortex-cerebellar interactions during learning of movement that accounts for experimental observations regarding the importance of sensory cortex input to the motor cortex and the relationship between the firing rate of motor cortex cells and the orientation of the hand in the workspace during movement. We are now extending our simulation to include consideration of the processing necessary to permit multiple motor cortex efferent zones to jointly control movement of both a simulated limb and a robotic manipulator within three-dimensional space. In addition we are undertaking further quantitative investigations to establish more precisely the extent to which the acquisition of novel motor skills may be determined by the type of model we have proposed.

BRTP UNIT: C

TITLE: Exploiting Diffusional Edge Enhancement to Measure Membrane Permeabilities

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

AXIS I: 9

AXIS II: 63c 77

INVEST1: Daniel Barsky
DEGREE1: PhD
DEPT1: Biophysics
NONHOST1:

INVEST2: Benno Pütz
DEGREE2: MS
DEPT2: Physics
NONHOST2:

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

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

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

% BRTP $: 6

ABSTRACT: We have previously demonstrated experimentally 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 relative enhancement of magnetization near these barriers in NMR microscopy. This enhanced magnetization can be exploited to determine characteristic properties of the barriers. Based on this effect, we developed a technique to measure the membrane permeability of red blood cells. We used a special diffusion weighting sequence to suppress all magnetization except in the immediate vicinity of the membranes. This allows us to measure an effective diffusion constant for a well defined region around the membranes. Compared to a similar method proposed earlier, our measurements show better agreement with permeability values obtained through measurements using contrast agents. This improvement may partly be explained by previously unexpected preserved magnetization *outside* the cells that was found through computer simulations.

In addition, the numerical techniques indicate that experimental observations should depend sensitively on the shape and orientation, but also the geometrical configuration of the cells. These factors determine the amount of magnetization preserved and what fraction of the magnetization outside the cells remains. They have to be understood in order to interpret mesurements.

Computer simulations of different geometric configurations of cell assemblies, carried out on the Resource's HP cluster, proved very helpful in understanding the microscopic mechanisms involved. Ongoing work aims at a more generally applicable description incorporating these geometric factors.

In an attempt to develop a coherent description of liposomal contrast agents we employed Monte Carlo simulations to compare and combine relaxation models based on susceptibility differences and on diffusion mediated relaxation.

	TECH RES & DEVEL (T)	COLLAB RES & SERVICE (C)	DISSEM & TRAINING (D)	TOTALS
NUMBER OF PUBLICATIONS	13	6	1	20
NUMBER OF SUBPROJECTS	5	5	1	11
NUMBER OF INVESTIGATORS	11	16	3	30[1]
PERCENT OF BRTP FUNDS ALLOCATED	44%	40%	16%	100%
SERVICE FEES COLLECTED	0	0	0	0
OTHER FUNDS ($)	640,000	150,000	–	790,000

[1]W. Humphrey is counted 3 times: once in the BRTP unit "T", once in the BRTP unit "C", and once in the BRTP unit "D". S. Tzonev is counted twice: once in the BRTP unit "T" and once in the BRTP unit "C".

State or Country	Number of Investigators
IL	24
IN	1
MD	1
CA	1
Israel	1
Germany	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
Erwin, Ed	University of Illinois (Schulten, Klaus)	FDN	
Feng, Zhou	University of Illinois (Schulten, Klaus)	FED	NIH
Hsu, Edward	Johns Hopkins University Hospital (Blackband, Stephan J.)	FED	NIH
Humphrey, William	University of Illinois (Schulten, Klaus)	SCCF	
Logunov, Ilya	University of Illinois (Schulten, Klaus)	FED OTH	
Malpelli, Joseph	University of Illinois (Malpelli, Joseph)	FED	NIH
Sheves, Mordechai	Weixmann Institute, Israel (Sheves, Mordechai)	OTH	
Obermayer, Klaus	University of Illinois (Schulten, Klaus)	FDN	
Pidgeon, Charles	Purdue University (Pidgeon, Charles)	FED OTH	NSF, NIH, Beckman
Pütz, Benno	University of Illinois (Schulten, Klaus)	FDN	
Schoeniger, Joseph J.	Sandia National Laboratories (Schoeniger, Joseph J.)	FED	DOE
Sheng, Qing	University of Illinois (Schulten, Klaus)	FED	NSF
Tzonev, Svilen	University of Illinois (Schulten, Klaus)	OTH	
Xu, Dong	University of Illinois (Schulten, Klaus)	FED	NIH

BRTP Unit T

Investigator	Non-Host Institution (Principal Investigator)	Sources of Support	
		TYPE	AGENCY
Bishop, Thomas	University of Illinois (Schulten, Klaus)	FED	NSF
Hesselroth, Ted	University of Illinois (Schulten, Klaus)	FDN	
Humphrey, William	University of Illinois (Schulten, Klaus)	SCCF	
Kale, Laxmikant	University of Illinois (Kale, Laxmikant)	FED	NSF NIH
Nelson, Mark	University of Illinois (Skeel, Robert)	FED	NIH
Shi, Joel	University of Illinois (Schulten, Klaus)	FED	NIH
Sinha, Amitabh	University of Illinois (Kale, Laxmikant)	FED	NIH
Skeel, Robert D.	University of Illinois (Skeel, Robert)	FED	NSF NIH
Tzonev, Svilen	University of Illinois (Schulten, Klaus)	OTH	
Wallace, Ken	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)	SCCF	
Kufrin, Rick	University of Illinois (NCSA)	FED	NSF

BRTP unit: (T)

NUMBER PUBLISHED –
Books: 0 Papers: 8 Abstracts: 0

NUMBER IN PRESS –
Books: 0 Papers: 5 Abstracts: 0

PUBLISHED:

* J. J. Biesiadecki and R. D. Skeel: "Danger of Multiple–Time–Step Methods", 1993.

* H. Heller, M. Schaefer, and K. Schulten: "Molecular Dynamics Simulation of a Bilayer of 200 Lipids in the Gel and in the Liquid Crystal-Phases", *J. Phys. Chem.*, **97**, 8343–8360 (1993).

* T. Martinetz and K. Schulten: "A Neural Network with Hebbian-Like Adaptation Rules Learning Visuomotor Coordination of a PUMA Robot", in "Proceedings of the IEEE International Conference on Neural Networks (ICNN–93), San Francisco", pages 820–825. 1993.

* T. Martinetz and K. Schulten: "Topology Representing Networks", **7**(3), 507–522 (1994).

* D. Okunbor and R. Skeel: "Canonical numerical methods for molecular dynamics simulations", *J. Comp. Chem.*, **15**, 72–79 (1994).

* A. B. Sinha, K. Schulten, and H. Heller: "Performance Analysis of a Parallel Molecular Dynamics Program", *Comput. Phys. Commun.*, **78**, 265–278 (1994).

* P. van der Smagt and K. Schulten: "Control of Pneumatic Robot Arm Dynamics by a Neural Network", in "Proceedings of the World Congress on Neural Networks, Portland, OR, July 11-15", Volume 3, pages 180–183, 1993.

* D. Xu and K. Schulten: "Coupling of Protein Motion to Electron Transfer in a Photosynthetic Reaction Center: Investigating the Low Temperature Behaviour in the Framework of the Spin-Boson Model", *Chem. Phys.*, **182**(2,3), 91–117 (1994).

IN PRESS:

* J. Biesiadecki and R. Skeel: "Simplectic integration with variable stepsize", Submitted.

* T. Bishop and K. Schulten: "Molecular Dynamics Study of a Sequence Specific Protein–DNA Interaction", in G. Wipff, Ed., "Computational Approaches in Supramolecular Chemistry". Kluwer, 1994, In Press. [Beckman Institute Technical Report TB-93-10].

* L. Kale: "Suggesting HPCC agendas", in U. Vishkin, Ed., "Application Oriented and Computer Science Centered HPCC Research". ACM Press.

* 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, In press. [Beckman Institute Technical Report TB-93-15].

* D. Xu and K. Schulten: "Temperature Quench Echoes and Velocity Reassignment Echoes in Proteins", *J. Chem. Phys.*, In Press. [Beckman Institute Technical Report TB-94-02].

BRTP unit: (C)

NUMBER PUBLISHED –
Books: 0 Papers: 3 Abstracts: 0

NUMBER IN PRESS –
Books: 0 Papers: 3 Abstracts: 0

PUBLISHED:

* J. M. Canfield, R. L. Belford, P. G. Debrunner, and K. Schulten: "A Perturbation Theory Treatment of Oscillating Magnetic Fields in the Radical Pair Mechanism", *Chem. Phys.*, **182**, 1–18 (1994).

* E. Erwin, K. Obermayer, and K. Schulten: "A Comparison of Models of Visual Cortical Map Formation", in F. H. Eeckman and J. M. Bower, Eds., "Computation and Neural Systems", chapter 60, pages 395–402. Kluwer Academic Publishers, 1993.

* W. Humphrey, I. Logunov, K. Schulten, and M. Sheves: "Molecular Dynamics Study of Bacteriorhodopsin and Artificial Pigments", *Biochemistry*, **33**, 3668–3678 (1994).

IN PRESS:

* E. Erwin, K. Obermayer, and K. Schulten: "Models of Orientation and Ocular Dominance Columns in the Visual Cortex: A Critical Comparison", Submitted.

* B. Pütz, D. Barsky, and K. Schulten: "Mechanisms of Liposomal Contrast Agents in Magnetic Resonance Imaging.", In Press. [Beckman Institute Technical Report TB-93-08].

* F. Zhou and K. Schulten: "Long Range Force Molecular Dynamics Study on Electrostatic and other Properties of a Membrane–Water Interface", Submitted. [Beckman Institute Technical Report TB-94-01].

BRTP unit: (D)

NUMBER PUBLISHED –
Books: 0 Papers: 1 Abstracts: 0

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

Published:

* W. Humphrey and A. Dalke: "VMD User Guide (Version 0.94)", Beckman Institute Technical Report TB-94-07, University of Illinois, 1994.

In Press:

Advisory committee

The Resource advisory committee met on April 11, 1994 in order to review success of past projects and provide advice on new research, technological directions, collaborations, and community needs.

The following colleagues served on the committee:

Chair: Christoph von der Malsburg, USC, Neurobiology, Max-Planck Institute for Brain Science, Frankfurt (Computational Neurobiology)
Bernie Alder, UC Berkeley, Physics (Computational Science)
Karl Hess, UIUC, Electrical Engineering (Computational Science)
Barry Honig, Columbia, Biochemistry (Computational Structural Biology)
Martin Karplus, Harvard, Chemistry (Computational Chemistry, Biology)
Attila Szabo, NIH

The next meeting of the advisory committee will take place in the spring of 1995. Until then the Resource intends to follow and implement the reccommendations made by the committee as outlined in the report, submitted to the NIH.

Dissemination and Training

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

In addition to the usual avenues of publication and invited lectures, we continue to run a seminar series 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).

As part of the GCAG collaborative efforts with researchers from Yale (A. Bruenger), NYU (T. Schlick), and Duke (J. Board) 13 Resource members participated in a meeting which took place in Pittsburgh in December of 1993. The meeting provided an appropriate setting for the exchange of information and ideas between the four research groups.

The 3D projection facility has been extensively used for scientific, dissemination and training purposes. The facility is regularly included on UIUC tours by federal and state officials. The facility is operated by the Resource personnel and demonstrations are made almost every day of the week. Recent visitors to the facility included R. Marcus, the Noble Prize winner; J. Yortner, President of the Israeli Academy of Science; Illinois Board of Higher Education; UIUC experimental groups such as A. Croft's; all seminar speakers to the Resource; and foreign delegations to UIUC.

The HP workstation cluster is being used by outside users such as A. Bruenger (Yale), J. Board (Duke) and other on-campus scientists.

The latest version of the program PMDi and the current documentation for PMDi are also available from the ftp site `ftp.ks.uiuc.edu`, directory `/pub/md`. The number of recorded retrievals of these items has increased in the past year and stands at 250.

A user manual, documentation and executable binaries for the program VMD are available from the ftp site `ftp.ks.uiuc.edu`, directory `/pub/vmd`.

A Mosaic server has been started to give access to all users of the internet to publications, images, and routine activities of the Resource. The address for the home page is `http://www.ks.uiuc.edu:1250/`.

An Open House was held for the first time on April 28, 1994 to present the Resource facilities. During the event the 3D projection facility, the HP workstation cluster, the robot arm, posters, and publications were demonstrated and presented. We intend to open our facilities to the UIUC community on a regular basis.

A two-month Resource summer school for nine prospective RAs, graduate students at the Physics and Chemistry departments on the UIUC campus, has been organized.

R. Skeel, together with J. Hermans, K. Kuczera, and B. Leimkuhler, is organizing a Workshop on Algorithms for Macromolecular Modeling to be held September 30–October 2, 1994 at the University of Kansas Institute for Theoretical and Computational Science in Lawrence. The emphasis is on the numerical and algorithmic challenges to achieving dramatic gains in the performance of software for protein and polymer simulations. Speakers include P. Bash, J. Board, R. Elber, P. Kollman, Z. Luthey-Schulten, M. Pettitt, C. Post, T. Schlick, K. Schulten, R. Scott, and P. Wolynes.

A workshop by Jan Hermans (UNC) is planned for the Fall and will be open for the Resource members and other interested scientists on the UIUC campus.

Outside Lectures

The PI presented the following invited lectures:

- July 25-30, 1993, 11th International Biophysics Meeting, Symposium "Macromolecular Biophysics"; Lecture: *Modeling Structure and Function of Proteins in Membranes*
- July 30-August 2, 1993, Symposium "Dynamics and Function of Biomolecules, Szeged, Hungary; Lecture: *Bacteriorhodopsin Structure Refinement and Investigations of its Photocycle by Molecular Dynamics Simulations*
- August 25-29, 1993, Symposium on Tunneling in the Condensed Phase at the 1993 Chicago American Chemical Society Meeting; Lecture: *Multi-Mode Protein-Electron Transfer Coupling*
- September 1-5, 1993, NATO Advanced Research Workshop: "Computational Approaches in Supramolecular Chemistry," Strassbourg, France; Lecture: *Modeling of energy transfer processes in membrane-protein water systems*
- September 17-18, 1993, University of Illinois, College Engineering Advisory Board (CEAB); Lecture: *The Role of Physics in Molecular Biotechnology*
- September 29-October 3, 1993, 2nd IUBMB Conference "Biochemistry of Cell Membranes," Bari, Italy; Lecture: *Molecular Dynamics Simulations of Membranes and Membrane Proteins*
- October 7, 1993, 2nd IMACS93 Conference on Computational Physics, St. Louis, Missouri; Plenary Lecture: *From Molecules to Networks: Grand Challenges in Biological Physics Demanding Computational Advances*

- October 29, 1993, University of Illinois, Group: CSRD Seminar; Lecture: *Molecular Dynamics on Parallel Computers*
- November 13, 1993, 2nd Britton Chance Research Discussion Meeting, Philadelphia, PA; Discussion participant on Coherent Phenomena; Excited States; Simulations; Microscopic Aspects of Electron Transfer session
- November 18-20, 1993, CECAM Workshop on "Protein Dynamics: The Convergence Between Simulation and Experiment' , Orsay, France; Lecture: *Spectral Lineshapes from Theory and Molecular Dynamics Simulations: NMR and Moessbauer Spectra, Electron Transfer Rates, Magnetic Field Effects*
- April 18-22, 1994 Joint April Meeting of the APS and the AAPT, Crystal City, VA; Lecture: *Echoes, Bends, and Twists in Proteins and DNA*
- May 11-14, 1994, Los Alamos National Laboratory; Lecture: *Molecular Dynamics Studies using Parallel Computers and New Algorithms: Membranes, Protein-DNA Complexes, Bacteriorhodopsin and Echoes*

The PI during the past year also served on the following committees:

- Computer Science Engineering Steering Committee, UIUC;
- Beckman Institute Program Advisory Committee;
- National Research Council Committee on the Future of Computer Science
- Appointment and Promotion Committee, Department of Physics, UIUC
- NIH Special Review Section, San Francisco, CA February 6-8, 1994
- Beckman Institute Human Computer Interaction Ad Hoc Committee
- Beckman Institute External Advisory Committee

Research personnel of the Resource during the past year have presented papers and posters at the following meetings and institutions:

- Gordon Research Conference, Wolfeboro, New Hampshire (Barsky, July 1993)
- Structure, Function and Development of the Visual System summer school, Cold Spring Harbor, NY (Tzonev, July 1993)
- Princeton Summer School in Biophysics, New Jersey (Logunov, July 1993)

- Conferences in Neuroscience IV: Motor Learning, Portland, Oregon (Wallace, August 1993)
- Workshop at SDSC, San Diego, California (Tzonev, August 1993)
- Workshop at NCSA, C-U, Illinois (Shi, Xu, August 1993)
- Mathematics of Computation 1943-1993: A half-century of computational mathematics, Vancouver, Canada (Zhang, August 1993)
- Biological Membranes Summer School, Vancouver, Canada (Zhou, August 1993)
- Computational Science Graduate Fellowship Conference, Minneapolis, Minnesota (Humphrey, August 1993)
- Cell and Molecular Biology/Molecular Biophysics, C-U, Illinois (Bishop, Logunov, Humphrey, Xu, Zhou, Barsky, September 1993)
- Fluctuations and Order Conference, Los Alamos (Kurrer, September 1993)
- NATO Advanced Research Workshop: "Computational Approaches in Supramolecular Chemistry," Strassbourg, France (Xu, Bishop September 1993)
- Integration Algorithms for Classical Mechanics, Waterloo, Ontario (Skeel, October 1993)
- Intel Supercomputer Conference, St Louis, Missouri (Humphrey, Bishop, Erwin, October 1993)
- Supercomputing 1993, Portland, Oregon (Humphrey, November 1993)
- NSF/GCAG Collaborative Retreat, PSC Pittspurgh, PA (Skeel, Kale, Sheng, Schulten, Bishop, Logunov, Humphrey, Nelson, Dalke, Xu, Wriggers, Zhou, Barsky, December 1993)
- Teraflop Computing and New Grand Challenge Applications, Baton Rouge, Lousiana (Bishop, Wriggers, February 1994)
- Workshop on Suggesting HPCC Agendas, Washington D.C. (Kale, March 1994)
- Biophysics Society Meeting, New Orleans, LA (Bishop, Logunov, Humphrey, Dalke, Xu, Wriggers, Zhou, Barsky, Puẽtz, April 1994)
- 27th Midwest Theoretical Chemistry Conference, Columbia, Missouri (Logunov, May 1994)
- Protein Engineering and Design, C-U, Illinois (Bishop. Humphrey, Logunov, Wriggers, Dalke, Zhou, Sheng, June 1994)

Resource Seminar

The following outside speakers have presented lectures at the Resource seminar series during the past year:

- Prof. Michael Finke, Institut fuer Logik, University of Karlsruhe, Germany, July 20, 1993. Lecture: *On the Estimation of A-Posteriori Probabilities Using Stochastic Networks*
- Dr. Patrick van der Smagt, University of Amsterdam, The Netherlands, July 22, 1993. Lecture: *A Neural Cyclops Learns to Grasp*
- Dr. Lutz Priese, Image Recognition Laboratory, Universitaet Koblenz-Landau, Germany, August 4, 1993. Lecture: *Hierarchical Color Segmentation and Applications in Traffic Sign Recognition*
- Prof. Helge Ritter, Department of Information Science, Bielefeld University, Germany, August 30, 1993. Lecture: *Self-organizing Maps and Neural Network Learning – Robotics as a Testing Ground*
- Prof. Ron Elber, University of Illinois at Chicago and The Hebrew University of Jerusalem, September 13, 1993. Lecture: *LES studies of short peptides in solution: CHDLFC and CAAAAC - do they have a unique structure?*
- Dr. Andreas Windemuth, Department of Biochemistry, Columbia University, September 20, 1993. Lecture: *Scalable Parallel Molecular Dynamics Simulation*
- Prof. Oren M. Becker, Department of Chemistry, Harvard University, October 4, 1993. Lecture: *Temperature Echoes in Molecular Dynamics Simulations of Proteins*
- Prof. Oleg Sineschekov, Department of Physico-Chemical Biology, Moscow State University, January 10, 1994. Lecture: *Light Reception and Signal Transduction in Unicellular algal Flagellates: Electrophysiological Approach*
- Prof. B.M. Odintsov, Academy of Sciences, Kazan, Russia, January 14, 1994. Lecture: *Optical-Detection ESR Tomography of Short-Lived Ion-Radical Pairs in a Radiation Track*
- Prof. M. Sheves, Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel, January 18, 1994. Lecture: *Bacteriorhodopsin Binding-Site Structure and the Role of the Retinal-Lysine Bond in the Pigment Photocycle*
- Prof. Charles Pidgeon, Department of Medicinal Chemistry, Purdue University, Visiting Professor, Beckman Institute, January 19-20, 1994. Lecture: *Understanding the Biology of HIV*

- Prof. Tom Ebrey, Department of Biophysics and Beckman Institute, University of Illinois, January 24, 1994. Lecture: *Molecular Mechanisms Operating in the Proton Pump Bacteriorhodopsin*

- Dr. Mark Millonas, Theoretical Division, Los Alamos National Lab and Sante Fe Institute, New Mexico, January 31, 1994. Lecture: *Nanoscale Thermodynamics, or, How to Build Nanoscale Engines*

- Prof. Elmar Wolff, Institute for Technology Development and Systems Analysis, University of Witten/Herdecke, Germany, January 31, 1994. Lecture: *Modeling Experimental 'Reality' in Biosciences by Object Oriented Programming: Bacteriotactic and Electric Signal Induced by Proton Pumping bR)*

- Prof. Michael Berry, Gordon McKay Laboratory, Harvard University, February 2, 1994. Lecture: *Coherent Backscattering and Quantum Chaos in the Electronic Transport of Ballistic Semiconductor Nanostructures*

- Prof. Walter Stoeckenius, Professor Emeritus, University of California San Francisco, February 14, 1994. Lecture: *The Bacterial Rhodopsins of Halobacteria*

- Dr. Klaus-Robert Mueller, GMD First, Berlin, Germany, February 16, 1994. Lecture: *Unsupervised Segmentation and Prediction of Non-Stationare Signals for Speech Recognition*

- Prof. Xiche Hu, Department of Chemistry, University of California-Irvine, February 21, 1994. Lecture: *Molecular Dynamics Studies of the Role of Microscopic Solvation in Association Reactions*

- Prof. Ernst-Walter Knapp, Free University of Berlin, Berlin, Germany, February 28, 1994. Lecture: *Long time dynamics of proteins with a Monte Carlo Method*

- Dr. Lennart Nilsson, Karolinska Institute Center for Structural Biochemistry, NOVUM Research Park, Huddinge, Sweden, March 3, 1994. Lecture: *Molecular Recognition: Simulation Studies of DNA Binding Proteins Free and in Complex with DNA*

- Prof. Michael Zeller, Physikalisches Institut, J.W.G. Universitaet Frankfurt, Lecture: *Nonlinear Dynamics in Neural Models* March 14, 1994.

- Prof. Stephen White, University of California-Irvine, March 21, 1994. Lecture: *Peptides in Bilayers: Structural and thermodynamic Basis for Partitioning and Folding*

- Prof. Steve Scheiner, Department of Chemistry and Biochemistry, Southern Illinois University at Carbondale, April 4, 1994. Lecture: *Principles of Proton Transfers*

- Prof. Charlie Anderson, Washington University, April 11, 1994. Lecture: *Representations Utilized in Neurobiological Sensory and Motor Planning Systems*

- Prof. L. L. van Hemmen, Department of Physics, Technical University of Munich, Germany, April 25, 1994. Lecture: *Hebbian unlearning of spatio-temporal patterns*

- Dr. Paul A. Bash, Research Scientist, Dept of Biology, Argonne National Laboratory, May 2, 1994. Lecture: *Computer simulation of the Enzyme Reaction in Malate Dehydrogenase using a combined quantum and molecular mechanics methodology*

- Prof. Mark S. Braiman, Department of Biochemistry, University of Virginia, May 9, 1994. Lecture: *Membrane Protein Dynamics from Infrared Spectra: Chloride and Proton Pumping Mechanisms of Halorhodopsin and Bacteriorhodopsin*

- Prof. Stephen Wassall, Associate Professor of Physics, Department of Physics, Indiana University-Purdue University Indianapolis, May 19, 1994. Lecture: *Solid State NMR Studies of Model Membranes*

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