# Department of Health and Human Services
# Public Health Service
# National Institutes of Health

## National Center for Resources
## Biomedical Research Technology Program

## Annual Progress Report

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| PHS Grant Number: | P41 RR05969 |
| Name of Recipient Institution: | Concurrent Biological Computing |
| Reporting Period: | |
| From: | 8/01/91 |
| To: | 7/31/92 |
| Principal Investigator: | |
| Klaus Schulten, PhD | |

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Signed: 28th September 1994


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The Resource for Concurrent Biological Computing exploits the opportunities which arise for computational biology through the advent of the massively parallel (concurrent) computer. It adopts a three-fold approach to concurrent computing, employing small scale parallel machines operated by the Resource, large scale parallel machines operated by National Centers, and networked workstations coordinated to behave as single computational devices. The Resource stresses software development, making its programs for parallel computers available to the community as well as developing new algorithms which, independent of hardware advances, achieved a great speed-up of computational tasks to be carried out in biological research. The main emphasis of Resource activities is on the actual use of novel hardware and algorithms for important research problems which require high performance computing. Key examples are the simulation of the enzyme phospholipase interacting with biological membranes (collaboration with Lilly Research laboratories), the development of a magnetic resonance imaging microscope (collaboration with researchers at John Hopkins Medical School and Sandia laboratories) and the modelling of the development of the visual cortex in macaque monkeys (collaboration with researchers at Harvard Medical School). The mentioned projects, described in the highlight section, constitute some of the most challenging research problems of modern medicine and biology while at the same time hinging on the availability of computational resources which today can only be provided through use of massively parallel machines.

We want to refrain from presenting the broader mission of the Resource in this year's progress report since our mission has been amply described in a detailed proposal text submitted October 1991 for renewal of funding for the Resource. Rather we cover in the present progress report the main projects of the Resource together with advances achieved after the renewal proposal had been submitted. The following sections cover six Resource projects which are prototypical for the collaborations of Resource personnel with outside groups and for the technical developments achieved towards the goal of advancing the computational frontier of modern biology and medicine.

# Accelerated Molecular Dynamics Simulation with the Parallel Fast Multipole Algorithm

The Fast Multipole Algorithm (FMA) of Greengard and Rokhlin [1, 2] was implemented to run in parallel as part of the molecular dynamics program MD [3] on a network of Workstations using the well-known coordination language LINDA [4, 5, 6, 7]. The implementation was done in collaboration with John Board from Duke University. The Fast Multipole Algorithm method allows the rapid computation of the non-bonded forces acting in dynamical protein systems without truncation or other corruption of the Coulomb forces, thereby surmounting one of the most prominent obstacles in the molecular dynamics simulation of large and very large systems.

Trial simulations have shown that the use of the non-parallel version of the algorithm speeds up simulations of protein systems with approximately 24,000 atoms by up to an order of magnitude on a single workstation. Preliminary benchmarks of the parallel network version demonstrate an efficiency of 85% on 4 workstations, larger networks are expected to yield efficiencies of 70% or more [8].

The LINDA implementation should enable us in the next funding period to port the program without difficulties to all systems that support LINDA, which range from networks to dedicated massively parallel supercomputers. In addition, the implementation is not particular to LINDA and can be easily reimplemented using a conventional message passing protocol. During the next funding period, we intend to use the message passing libraries of the Connection Machine CM-5 in the process of porting the program MD to that machine.

# Parallel Molecular Dynamics Program for MIMD-type Computers

A parallel programming system called CHARM [9, 10] has been developed in the Computer Science Department of the University of Illinois by L. V. Kale. This system is intended to provide portable parallel programming across all MIMD machines, and is particularly aimed at large message-passing machines. CHARM provides support for dynamic [11] as well as static load balancing.

CHARM currently runs on "multicomputers" including Intel's iPSC/860, iPSC/2, and NCUBE/two (on which it has been tested with up to 1024 processors). It runs on shared memory machines such as a Sequent Symmetry, an Alliant, an Encore Multimax, etc., and is being ported to a network of workstations and the BBN butterfly machines. Programs may be run without change on any of these machines, with occasional minor performance tunings.

We have ported the molecular dynamics programm EGO , which was originally written in occam II and ran only on Transputer machines, to the C language and CHARM. This enables a wider audience of researchers to use EGO as a computational tool in their research. In a concurrent effort we are porting EGO to the new Connection Machine CM-5, where it utilizes the MIMD-mode of the CM-5 and the message passing libraries of Thinking Machines Corporation. Both efforts will continue into the next funding period.

# Distributed Interactive Molecular Dynamics

This project is carried out in collaboration with Mike Krogh (visualization specialist, National Center for Supercomputing Applications) and Rick Kufrin (supercomputer application specialist, NCSA). Presently, there are several excellent molecular visualization packages available (Polygen Quanta and Biosym for the SGI, CAChe and MacImDad for the Macintosh II, Midas Plus [12, 13] for NeXT and SGI). However, none allow for direct visualization of a molecule as it is simulated; all require the generation of intermediate data files. The goal of this project is to provide a visualization program running on a graphics workstation, and replace the intermediate data files with a direct network connection to a supercomputer running a molecular dynamics (MD) simulation package. The visualization program can act as a 'master', and provide a user interface to the researcher to allow interactive control of the parameters and state of the simulation being done remotely. The user will be able to choose the remote machine to use for dynamics calculation, the molecule to simulate, and have the simulation run with an on-line display of the current state of the molecule.

Currently, all development is being done using a Silicon Graphics VGX-class workstation for visualization, the CM-200, and the Resource's MD library [3] for calculation. A demonstration program has been developed to test the methods planned for this project; this demo program showed the feasibility of having a shared memory and Internet network link between an SGI and CM-200, having MD simulation data passed to the SGI, and having simulation results displayed using the SGI screen. Software is also being developed to use the virtual reality equipment currently operated by NCSA; this would provide a true three-dimensional environment for molecular dynamics interaction. This demonstration program is currently being used as a basis for a new program to incorporate a standard user interface and set of interactive commands for all display devices. Additionally, a software module resident on the CM-200 will interpret commands from the SGI and pass MD simulation data back to the SGI. A demonstration of this new program will be given at the Showcase exhibit at SIGGRAPH '92 in Chicago. It is planned to provide the capability of using the Cray 2, CM-5, the Resource's Transputer-based parallel computer of the Resource, and networks of workstations for calculation.

# Interaction of Phospholipase $A_2$ with a Membrane Surface

The structure of membrane proteins, signal transduction, ion channels, protein–lipid and peptide–lipid interactions are only a few examples of membrane related processes of great biological importance. At the same time, these processes are of major relevance to pharmaceutical research. To understand these at an atomic level it is necessary to be able to handle the simulation of large heterogeneous systems with several tens of thousands of atoms, a task that requires the use of massively parallel computers.

As a basis for our studies of membrane related processes, we have constructed a bilayer membrane system with 68 Å × 75 Å lateral dimension. The system consists of 200 phosphatidyl–choline molecules and 4526 water molecules covering the two surfaces of the bilayer. An 8 Å stochastic boundary [14] is used to exclude the possibility of system disintegration. We have equilibrated the system over a timespan of more than 120 ps using the parallel transputer machine of the Resource [15]. Subsequently, we have analyzed the equilibrated structure and the trajectory of the bilayer. We found good agreement between experimental data and the results of our analysis, e. g., the order parameter profile of the lipid tails and the tilted configuration of the lipid headgroups [16, 17]. The coordinates of the equilibrated membrane–water system are available to the research community via anonymous ftp from lisboa.ks.uiuc.edu.

Phospholipase $A_2$ is one of the most intensively studied membrane proteins which hydrolyzes phospholipids at the sn-2 position to form fatty acid and lysophospholipid products [18]. These are small proteins and the 3-D structures are known to high resolution for several species [19]. Phospholipase $A_2$ is of high pharmaceutical concern since it is responsible for the release of arachidonic acid from membranes, and since the subsequent conversion of this fatty acid to leukotrienes and prostaglandins is part of the inflammatory response. The enzyme also shows very interesting interactions with the membrane on which it binds [20]. It is activated and exerts much higher catalytic activity when it interacts with aggregated forms of the substrate, such as in micelles or in bilayers.

In collaboration with Dr. Robert B. Hermann of the Eli Lilly and company, we intend to study the interaction of the enzyme with biological membranes and provide insights for inhibitor design for the enzyme. The protein-membrane system consists of more than 10,000 aoms, and computational studies would be impossible to carry out without the computational facility at the resource. In the first stage, we are more focused on obtaining a model of the enzyme-membrane complex and on understanding the energetic contributions which causes the membrane binding. Another objective for the current work is to study the effects of membrane binding on the enzyme-substrate association process, which is suggested to cause the enzyme activation on the membrane surface.

# Diffusional Edge Enhancement in Nuclear Magnetic Resonance Microscopy

We have experimentally and theoretically demonstrated that, in the presence of a standard magnetic field gradient, diffusional barriers in the imaged volume will result in the enhancement of magnetization near barriers. We have observed halos of enhanced intensity in cross sectional images of cylindrical capillary tubes. In collaboration with Joseph Schoengier, Edward W. Hsu, and Stephan Blackband, we have made systematic experimental observations of diffusional edge enhancement in one- and two-dimensional Fourier encoded NMR microscopy and the results compare well with numerically intensive Monte Carlo simulations, carried out on high performance computers at the resource [21].

This edge enhancement potentially provides a means whereby NMR microscopy can be used to visualize small impermeable structures that might otherwise be invisible, and may provide a means for detecting boundaries in NMR micrographs, even when the actual boundaries themselves cannot be resolved. In addition to applications in imaging, this effect could potentially be exploited to study a variety of processes occuring in inhomogeneous liquid/solid samples, such as surface catalyzed chemical reactions, relaxivity of surfaces, or mobility of spins near surfaces, because it allows one to obtain a spectroscopic signal from only those spins near surfaces—the nearness depending on the diffusion coefficient of the bulk liquid and the parameters of the NMR pulse sequence.

# Structure, Function and Models of Formation of Visual Cortical Maps

In the primary visual cortex (area 17) of mammals, most neurons respond best to elongated visual stimuli presented to a particular eye at a particular retinal location. Nearby cortical cells tend to have similar feature preferences, thus forming a map-like structure. During the last few years, a method called optical imaging has been developed, making it possible to obtain high-resolution images of these visual cortical maps [22, 23]. At the same time, high-performance parallel computers have become available which allow for the first time the testing of hypotheses on these brain structures in detail. The aim of this project is to combine these novel experimental and computational techniques in a collaborative effort between neurophysiologists — including the group of G. G. Blasdel of Harvard Medical School — and the resource staff, to shed more light on the structure, function and development of cortical maps. We developed a neural-network model based on Kohonen's self-organizing feature map algorithm to better understand the development of the retinotopic maps, and orientation and ocular-dominance column maps in the primary visual cortex of monkey and cat [24, 25]. The model describes the development of these patterns as an unsupervised learning process, where visual stimulation drives the emergence of feature-selective cells. The model has been implemented on parallel computers [26] to allow large-scale numerical studies of pattern formation. Model maps reproduce several of the features characterizing the spatial structure of cortical maps [27], including the correlations between the orientation and ocular dominance systems recently found in experimental data, which we have access to through our collaboration with G. G. Blasdel. Analytical studies [27, 28, 29] of the neural network model have revealed the processes by which the algorithm forms ordered maps. We also study alternative models of cortical map formation, such as those due to K. Miller [30], N. Swindale [31], Durbin and Mitchison [32], Rojer and Schwartz [33], and others, using parallel computers. In several cases we have extended the originally-proposed models so that their predictions may be compared with each other and with the experimental data. This work is performed in collaboration with Mark Nelson of the University of Illinois, and we cooperate with Ken Miller as well, who now uses our parallel implementation of his model. These ongoing studies have indicated that only a few simple, biologically-plausible assumptions are sufficient to account in detail for the observed spatial structure of brain maps in the visual cortex. In addition we study the functional significance of the map structures through the use of a detailed cortical neural simulator — originally developed for the Connection Machine in the group of C. Koch [34], and now running on our machines — in which we configure the connections between neurons and retinal cells in ways suggested by the structure of the model maps developed above. This study could lead to a better understanding of the purpose behind the observed organization of visual cortex.

# Interaction of Phospholipase $A_2$ with a Membrane Surface

Membrane proteins and membrane related processes have been the subject of intensive research during the past years, both experimentally [35] and theoretically [36, 37, 16, 38, 39, 40].

One reason for the relatively low interest of the theoretical community in investigating membranes may have been the lack of detailed structural information on membrane proteins and the statistical nature of lipid structure which implies the need for studying either large systems and/or long time ranges. Also, until recent years researchers were generally restricted to molecular dynamics studies of proteins *in vacuo* because of limitations in computational power [41, 42, 43, 44]. There is evidence, however, that the environment has a strong influence on the structure and function of proteins, both in solution and in membranes [45, 46, 47, 48, 40].

Early theoretical investigations of membranes were done by Marčelja [36] who introduced a molecular field model to represent the influence of neighboring lipid molecules. One drawback of this model is that it cannot reproduce cooperative effects of several lipid molecules. As computers became more powerful, MD simulations of small systems (2 x 16 decanoate molecules) over short times on the order of 100 ps became feasable [49]. However, the periodic boundary conditions together with the small system size gave rise to artifacts which were reduced in later studies by increasing the system size to 2 x 64 decane molecules [50]. Another improvement was the inclusion of water and ions in the simulation [51]. Besides monolayers and bilayers, micelle-water systems have also been simulated [52, 53].

The time range of the simulations listed above is on the order of 100 ps. This severely limits the investigation of many membrane properties, e.g. phase transitions, which occur on time scales in the range of microseconds and longer. A combination of Brownian dynamics with the Marčelja molecular field model allowed the simulation of a single chain of a DPPC molecule for 0.66 $\mu$s [54, 55]. Here too, one improvement was to increase the size of the system [39, 56] to 7 molecules at present.

One extremely promising idea of applying theoretical membrane studies is to use the simulated systems as a basis for studying membrane–protein interactions [45]. With modern supercomputers, especially parallel machines [57, 3], providing computing power in the gigaflop range, and with the development of efficient algorithms [58, 59, 1, 60], the study of large and heterogeneous systems using molecular dynamics has become increasingly feasible. Here we report on the construction and molecular dynamics study of a $66 \times 80$ Å$^2$ piece of a membrane bilayer covered with up to 15 Å of water on each side. The system was specifically designed to accomodate a membrane protein of about 20,000 molecular weight, e.g. *bacteriorhodopsin*, and can easily be extended.

Our first interest in protein-membrane interaction is focused on a small lipid-digesting enzyme, phospholipase $A_2$ (PLA), which binds and scoots on the membrane surface and cleaves the *sn*-2 ester bonds of the lipid. PLAs are water soluble, stable and rigid proteins with about 120 amino acids in a single peptide chain. PLAs from various species all have an absolute requirement for calcium. The lipid digesting reaction is catalyzed by a catalytic triad formed by conserved His, Tyr, and Asp residues, very similar to the catalytic system of serine proteases [61]. X-ray structures [19, 62, 63] revealed a common 3-D architecture. The enzyme has a hydrophobic substrate binding pocket, which fits tightly and positions the substrate in precise geometry to be cleaved. The enzyme also has another hydrophobic region, which forms a flat surface of the protein and is surrounded by polar and positive residues. This surface is involved in the membrane-binding process and is called interface recognition surface (IRS). Kinetic studies of the enzyme reaction on membrane bilayers are reported in [20]. Once the enzyme binds to the membrane, it cleaves thousands of lipid molecules in a scooting mode before dissocating from the membrane. The turn over rate of the membrane-bound enzyme is several orders of magnitude larger than the rate of the unbound enzyme. Very little is still known of the enzyme-membrane complex structure and why the enzyme reacts more efficiently once it binds its substrates in an aggregated form.

We are also interested, in a later stage, to assist inhibitor design for the enzyme through computational studies. Dr. Robert B. Hermann, a senior computational chemist, is collaborating with us on this project. Since the protein-membrane-water system consists of more than 10,000 atoms, simulation studies is only practical when carried out using supercomputers. Preliminary work has been carried out on the Cray-2 provided by NCSA, where a 100 ps simulation takes 60 hours of Cray time. We expect that future work on inhibitor design and free energy calculations will require much longer computation time. Massively parallel computers, such as the CM-5, are probably needed to accomplish these simulations in a reasonable amount of time.

Currently, we are focused on more basic and biological questions concerning the protein-membrane interaction, such as:

(1) Why and how does the enzyme bind to the membrane surface? Phospholipase $A_2$ is a highly positively charged protein, and it binds preferentially to anionic membranes. Electrostatic interaction is clearly very important in the enzyme–membrane binding process. It is known from experiment that the enzyme contacts the membrane using the IRS surface. The opposite surface of the enzyme is also flat but consists of more hydrophilic and charged residues. We presently investigate why the enzyme binds the membrane using the more hydrophobic IRS region, and what changes occur to lipid head groups once the lipid is desolvated by the protein.

(2) What are the differences in structure and dynamics of the enzyme on the membrane as

compared to the enzyme in solution? As the enzyme binds to the membrane, the residues on the IRS surface are closely packed to the membrane. Experiments have shown that the motion of residue Trp-3, which is in contact with the membrane, is severely restricted in the enzyme-membrane complex. It is of interest to see whether the dynamic property of the whole protein is affected after binding to the membrane, and how membrane binding affects the protein residues in contact with the membrane.

(3). How is the lipid substrate bound to phopholipase $A_2$ in solution and on the membrane? A few models have been suggested in the literature to explain the remarkable increase in the enzyme turnover number once it binds to the membrane. It is suggested that the desolvation of the lipid head group in the enzyme-membrane complex lowers the free energy barrier for the binding process. Also, the more confined geometry of lipid in the membrane might also facilitate its diffusion through the hydrophobic entrance. We intend to carry out free energy calculations for the substrate dissociation process both in solution and on the membrane.

We have completed the construction of a membrane monolayer of 60 DPPE molecules. The membrane was then simulated together with the phospholipase $A_2$ molecule and 2373 water molecules. In the first simulation, phospholipase was put above the membrane without close contact. The closest distance between the protein and the membrane atoms was larger than 5 Åin the initial structure, and about 3 layers of water were present between the protein and the membrane. The system was equilibrated and thermalized and a 100 ps molecule dynamics run was carried out. Another simulation was then completed using the same procedure for phospholipase $A_2$ in close contact with the membrane. Figure 1 presents the protein phospholipase docked to a membrane patch. The structure shown is the first result of a simulation of the action of phospholipase on a membrane. The results indicate that the binding of the enzyme is facilitated by favorable Coulomb interactions, hydrophobic interactions, as well as through hydrogen bonds between the membrane and protein polar groups. It appears that the binding is not due to specific interactions at one or two sites, but rather is due to multiple interactions between the enzyme and the membrane. We have also employed an electrostatics program developed at the resource [64] to eveluate the binding enthalpy due to electrostatic contributions.

Figure 1: First results of bovine phospholipase $A_2$ docked to a monolayer of the bilipid membrane. The protein residues are colored according to its polarity (red: acidic, cyan: basic, yellow: polar, white: nonpolar). The DPPE lipid head groups are colored as following: the terminal amino group colored cyan, oxygen atoms colored red, and the phosphorus atoms colored yellow. The figure demonstrates that a first simulation of the phospholipase interacting with a lipid membrane has been achieved.

# Diffusional Edge Enhancement in Nuclear Magnetic Resonance Microscopy

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. 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 regions 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 Joseph Schoengier, Edward W. Hsu, and Stephan Blackband, 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 [65]. Previous theoretical analyses [65, 66] indicate that this decrease would result in relative motional narrowing of the resonances of water spins, for example, proximate to the wall of a cylindrical capillary tube, which then would result in a ring of enhanced intensity in projection-reconstruction cross sectional images. Moreover, because spins near barriers are on average less displaced, they are less dephased by a field gradient, and the partial retention of phase coherence can lead to a high magnetization intensity near boundaries. We have made systematic experimental observations of diffusional edge enhancement in one- and two-dimensional Fourier encoded NMR microscopy and the results compare well with calculations based on Monte Carlo simulations of diffusing and precessing spins [21]. The numerically intensive simulations have been performed on networks of workstations available on-site at the Resource.

Figure 2 (a) shows the magnetization profile after diffusion weighting and Fourier encoding along a direction perpendicular to a capillary. The edge enhancement appears as two prominent peaks. We imaged the capillary by the usual 2DFT reconstruction method. See Fig. 2 (b). Two sickle-shaped maxima are clearly visible at the boundaries along the frequency-encoding axis (skew horizontal axis in image) while no distortion can be seen in the orthogonal direction of the phase-encoding gradient.

This edge enhancement potentially provides a means of visualizing, through NMR microscopy, small impermeable structures that might otherwise be invisible against a background of freely diffusing spins. This is a potential technique for contrast enhancement in NMR microscopy, and may provide a means for detecting boundaries in NMR micrographs, even when the actual boundaries themselves cannot be resolved. We have demonstrated, both experimentally and theoretically, that under suitable conditions, a bipolar gradient pulse may be used to annihilate any magnetization which is not imme-

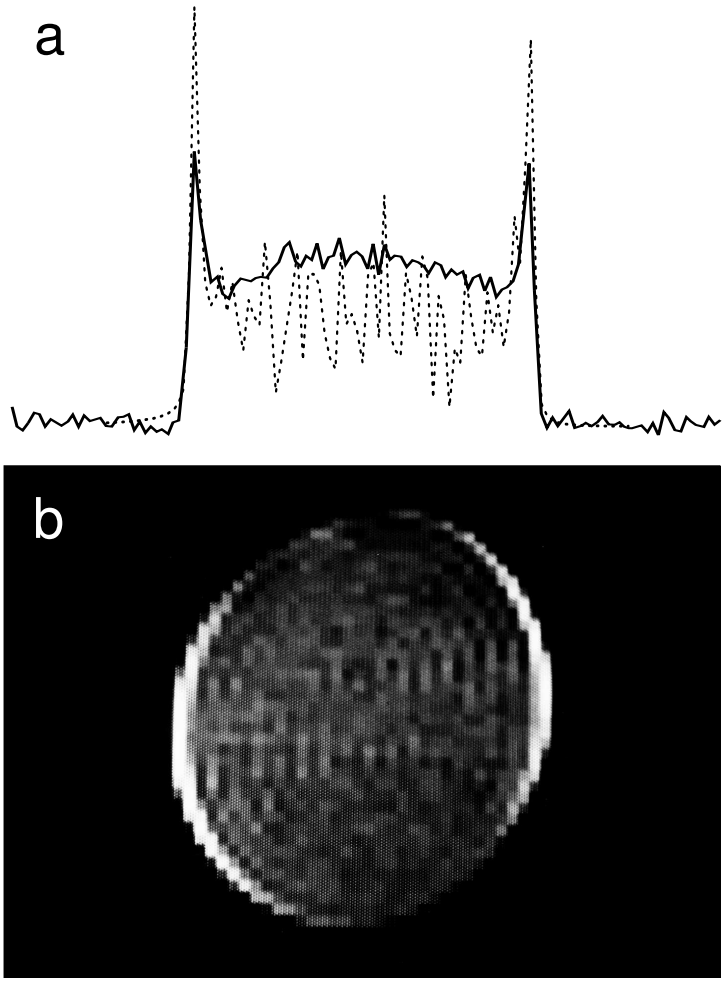


Figure 2: NMR microscopy of a 600 $\mu$m water-filled glass capillary. (a) Observed (solid) and simulated (dotted) magnetization profile by Fourier transform of the FID signal. (b) Observed 2DFT reconstruction.

diately proximate to a boundary. In addition to applications in imaging, this effect could potentially be exploited to study a variety of processes occuring in inhomogeneous liquid/solid samples, such as surface catalyzed chemical reactions, relaxivity of surfaces, or mobility of spins near surfaces, because it allows one to obtain a spectroscopic signal from only those spins near surfaces—the nearness depending on the diffusion coefficient of the bulk liquid, and the gradient strength and duration employed in the pulse sequence. The effect should not only occur near impermeable barriers, but near any region of abrupt transition in diffusion coefficient. This work provides the understanding needed to avoid such effects where they are not desired, as well as to exploit edge enhancement effects for imaging microscopic structures in tissues and biological samples, such as bone matter, cells, or possibly even cell organelles.

# Structure, Function and Models of Formation of Visual Cortical Maps

Mammalian visual cortex is functionally organized in map-like structures. In the primary visual cortex (area 17), most neurons show a preference for elongated visual stimuli presented to a particular eye, and nearby cortical cells tend to have similar feature preferences. The spatial organization of these feature preferences may be seen in Figure 3 (a). The data for this figure was obtained from macaque striate cortex using voltage-sensitive dyes in an optical imaging technique [22], and comes from the research group of G. G. Blasdel (Harvard Medical School), who collaborates with resource staff on this project. Although not shown in the figure, maps of other stimulus features, such as retinal location and velocitiy preference for moving stimuli, co-exist in the same cortical region.

Figure 3: **(a)** Left column: Experimentally-observed orientation (top) and ocular dominance (bottom) columns in a 6 $mm \times 4$ $mm$ patch of monkey striate cortex, located near the area 17/18 border. (Data from the research group of G. G. Blasdel.) **(b)** Right column: Model orientation and ocular dominance columns generated by the self-organizing feature-map model. For the orientation column maps, each color codes for a particular preferred visual stimulus orientation, with brightness level indicating the (normalized) degree of preference for a particular orientation. Light and dark pixels in the ocular dominance column maps indicate preference for left- or right-eye stimulation.

A neural-network model, based on Kohonen's self-organizing feature map algorithm, has been developed to better understand the development of these retinotopic maps, and orientation and ocular-dominance columns in the primary visual cortex of monkey and cat [24, 25]. The model describes the development of these patterns as an unsupervised

learning process, where visual stimulation drives the emergence of feature-selective cells. The model has been implemented on parallel computers [26] — a Transputer-based (T800) system, and a Connection Machine CM-2 — to allow large-scale numerical studies of pattern formation.

The model was studied with various assumptions about the input patterns driving map formation, including pattern distributions resembling sensory deprivation experiments. It reproduces several of the features characterizing the spatial structure of cortical maps [27] (see Figure 3 (b)), e.g., the hierarchical mapping of position vs. orientation and ocular dominance, the slab- and foci-like regions in the orientation map, the correlations between fractures, foci, and orientation specificity, and correlations between the orientation and ocular dominance systems recently found in the experimental data. Different parameters produce model maps which compare well with experimental maps from macaque monkeys and cats of different ages. Analytical studies of the neural network model have indicated that the formation of ocular dominance and orientation column systems is the result of an instability of the retinotopic projection under visual stimulation [27], and have revealed the processes by which the algorithm works to form the ordered mapping [28, 29]. The model has led to new predictions of, among other things, the fine structure of the retinotopic projection, which can be detected experimentally.

Many other models of the formation of these cortical maps have been proposed, e.g. [30, 31, 32, 33]. Although they are often based on quite different principles, and are formulated in very different algorithms, many of these models seem equally successful at accounting for the observed structure of cortical maps. In ongoing research performed in collaboration with Mark Nelson (University of Illinois), we are conducting large-scale simulations with several representative models from different model classes. These numerical studies have demonstrated that only a few simple, biologically-plausible assumptions, like Hebbian learning, and global competition and local cooperation between neurons during learning, are sufficient to account in detail for the observed spatial structure of brain maps in the visual cortex.

BRTP UNIT: T

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

KEYWORDS: MD, Linda, CM-5, networks of workstations

AXIS I: 2 9

AXIS II: 42 74

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% BRTP $: 15

ABSTRACT: The Fast Multipole Algorithm was implemented as part of the molecular dynamics program MD to greatly accelerate the simulation of biological macromolecules without neglecting important Coulomb interactions. The algorithm was compared to the direct method of determining the Coulomb force field of biological macromolecules and was found to be accurate, while providing a ten-fold increase in speed for a 24,000 atom system. Since the complexity of the algorithm is linear, we expect much larger savings for bigger systems. A parallel version of the program was also tested and shown to run efficiently on a small network of workstations, promising greater efficiencies for larger networks yet to be tested. The parallel version was implemented using the coordination language Linda. Further implementations are planned.

BRTP UNIT: T

TITLE: Parallel Molecular Dynamics Program for MIMD-type Computers

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

AXIS I: 9 11

AXIS II: 42 70

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% BRTP $: 25

ABSTRACT: We have ported the molecular dynamics program EGO for MIMD parallel computers to the C language to enable a larger group of researchers who have not ready access to Transputer-based computers, to employ this program. Since the C-version of EGO is built upon the CHARM coordination language, which provides a uniform programming environment across different machines and architectures, it can run on networks of workstations and shared memory as well as distributed memory machines.

BRTP UNIT: T

TITLE: Distributed Interactive Molecular Dynamics

KEYWORDS: graphics,network

AXIS I: 9 11

AXIS II: 42

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NONHOST2:

INVEST3: R. Kufrin
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DEPT3: National Center for Supercomputing Applications
NONHOST3:

% BRTP $: 15

ABSTRACT: Current methods for visualization of molecular dynamics simulations involve a multi-step process to convert simulation data to a displayable format. We are currently developing a single distributed environment for molecular dynamics simulations and visualization, to eliminate several steps in this process. Molecular dynamics programs running on a supercomputer are connected via network software to a control program running on a Silicon Graphics VGX-class workstation, to provide a single user interface to the molecular dynamics simulation and display. This program allows interactive control of the parameters and state of the simulation and provides a graphical visualization of the current state of the dynamics. Support for several display systems is provided, including virtual reality hardware, and SGI stereo display. Currently the system supports an interface with the Connection Machine 200; future extensions for connection to the Cray-2, CM-5, and networked workstations are planned.

BRTP UNIT: C

TITLE: Construction, Molecular Dynamics Simulation and Analysis of a Lipid Bilayer

KEYWORDS: phosphatidylcholine, aqueous environment, membrane, stochastic boundary simulation

AXIS I: 6

AXIS II: 74F

INVEST1: H. Heller
DEGREE1: Dipl.-Phys.
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INVEST2: M. Schaefer
DEGREE2: PhD
DEPT2: Biophysics
NONHOST2:

% BRTP $: 11.25

ABSTRACT: We have constructed and investigated a membrane–water system to provide a basis for theoretical investigations of membrane proteins, e. g., lipid–protein interactions or the equilibration of structural models. This system consists of 200 molecules of 1-palmitoyl-2-oleoyl-phosphatidylcholine forming a rectangular piece of a bilayer and of 4526 water molecules covering the lipid headgroups on each side. The total number of atoms is about 24,000. The lateral dimensions of the bilayer are 65 Å×85 Å, and the distance between the bilayer surfaces as given by the average phosphorus to phosphorus distance is 60 Å. The thickness of each water layer is up to 15 Å. After initial minimization, we performed a 160 ps molecular dynamics simulation. To prevent system disintegration, atoms within 8 Å from the surface were hamonically 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 equlibrate the system and to achieve a low, positive internal pressure. From the final 40 ps, we deduced quantities such as the order parameter profile, the average area per lipid molecule, and lipid self-diffusion coefficients. The extracted parameters are in reasonable agreement with experimental data and indicate that the simulated membrane is in the liquid crystal state. Our findings show that the simulated bilayer–water system has reached equilibrium and may be used as a template in future studies of membrane related processes and compounds.

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: 74H 74F

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

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

% BRTP $: 11.25

ABSTRACT: Interaction betweeen Phospholipase $A_2$ and membrane has received remarkable interests because of the biological importance of protein–membrane interaction and the pharmaceutical interests of this enzyme. We have constructed a monolayer of 60 Dipalmitoyl Phosphotidylethanolamine (DPPE) molecules and simulated the enzyme-membrane-water system which consists of 10881 atoms using the program X-PLOR on the Cray-2 machine provided by NCSA. The protein has been put in the system in 2 different ways, above the membrane without direct contact, in contact with the membrane with the hydrophobic surface (IRS region). A third simulation with Phospholipase $A_2$ in contact with the membrane with the hydrophilic surface will be carried out shortly. All simulations are done using the same procedure of equilibration and thermalization and with a periodic boundary. We intend to further compare the energetics of the system in these simulations and understand the mechanism of the binding process. We also intend to study the substrate binding process of the enzyme in different environments through free energy calculations.

BRTP UNIT: C

TITLE: Diffusional Edge Enhancement in Nuclear Magnetic Resonance Microscopy

KEYWORDS:

AXIS I: 9

AXIS II: 63c 77

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

INVEST2: B. Pütz
DEGREE2: Dipl.-Phys.
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 $: 11.25

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. In samples there may exist regions that differ markedly in the translational diffusion coefficient of the molecules whose spatial distribution is being imaged. In particular, samples may contain 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. The observed effects are due simply to diffusional barriers, not compartmentalization. This edge enhancement potentially provides a means to use NMR microscopy for visualizing small, impermeable structures that might otherwise be invisible.

BRTP UNIT: C

TITLE: Structure, Function and Models of Formation of Visual Cortical Maps

KEYWORDS:

AXIS I: 21

AXIS II: 41 60 77 84

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

INVEST2: K. Obermayer
DEGREE2: PhD
DEPT2: Physics
NONHOST2:

INVEST3: G.G. Blasdel
DEGREE3: PhD
DEPT3:
NONHOST3: Harvard Medical School

INVEST4: M. Nelson
DEGREE4: PhD
DEPT4: Neuroscience
NONHOST4:

% BRTP $: 11.25

ABSTRACT: Mammalian primary visual cortex is functionally organized in map-like structures, with response properties of neurons — e.g., preferred retinal location and orientation of visual stimuli, and ocular dominance — mapped in a characteristic way across the cortical surface. A neural-network model, based on Kohonen's self-organizing feature map algorithm, has been developed to better understand the development of these map systems [24, 25]. The model has been implemented on parallel computers to allow large-scale numerical studies of pattern formation [26]. The model reproduces several of the features characterizing the spatial structure of cortical maps in macaque monkey or cat [27], including the correlations between the orientation and ocular dominance systems recently found in the experimental data, and has

led to new predictions of the fine structure of the retinotopic projection, which can be tested experimentally. Analytical studies [27, 28, 29] of the model indicate that the formation of column systems is the result of an instability of the retinotopic projection under visual stimulation, and explain what mechanisms drive the model algorithm to form the ordered mapping. We are also conducting large-scale simulations with several representative models from different classes of the many other models proposed for the development of visual cortical maps, e.g. [30, 31, 32, 33]. These numerical studies have demonstrated that only a few simple, biologically-plausible assumptions, like Hebbian learning, and global competition and local cooperation between neurons during learning, are sufficient to account in detail for the observed spatial structure of brain maps in the visual cortex. In addition we study the functional significance of the map structures through the use of a detailed cortical neural simulator, in which we configure the connections between neurons and retinal cells in ways suggested by the structure of the model maps developed above. This study could lead to a better understanding of the purpose behind the observed organization of visual cortex.

| | TECH RES & DEVEL (T) | COLLAB RES & SERVICE (C) | DISSEM & TRAINING (D) | TOTALS |
|---|---|---|---|---|
| **NUMBER OF PUBLICATIONS** | 49 | 3 | 1 | 53 |
| **NUMBER OF SUBPROJECTS** | 3 | 4 | 0 | 7 |
| **NUMBER OF INVESTIGATORS** | 8 | 13 | 0 | 21[1] |
| **PERCENT OF BRTP FUNDS ALLOCATED** | 45% | 45% | 10%[2] | 100% |
| **SERVICE FEES COLLECTED** | 0 | 0 | 0 | 0 |
| **OTHER FUNDS ($)** | 50,000 | 25,000 | – | 75,000 |

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

[2]This amount is included in the subproject form for "Parallel Molecular Dynamics Program for MIMD-type Computers"

| State or Country | Number of Investigators |
|---|---|
| IL | 13 |
| IN | 1 |
| MA | 2 |
| MD | 2 |
| NC | 1 |
| NM | 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 | |
| Chapron, Yves P.[3] | Commissariat a l'energie atomique (Dupont, Yves) | FED | CEA, DSV, CNRS |
| Erwin, Ed | University of Illinois (Schulten, Klaus) | FDN | |
| Feng, Zhou | University of Illinois (Schulten, Klaus) | FED | NIH |
| 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 |
| Nelson, Mark | University of Illinois (Nelson, Mark) | FED | NIMH |
| | (Gabriel, Mike) | FED | NSF |
| | (Bodznick, Dave) | FED | NSF |
| Obermayer, Klaus | University of Illinois (Schulten, Klaus) | FDN | |
| Pütz, Benno | University of Illinois (Schulten, Klaus) | FED | NIH |
| Schaefer, Michael | University of Illinois (Schulten, Klaus) | IND | |
| Schoeniger, Joseph J. | Sandia National Laboratories (Schoeniger, Joseph J.) | FED | DOE |

[3]Yves Chapron is a user of our Transputer guest account and of our molecular dynamics program EGO . Therefore he is not listed in any of the subproject forms.

# BRTP Unit T

| Investigator | Non-Host Institution (Principal Investigator) | Sources of Support | |
|---|---|---|---|
| | | TYPE | AGENCY |
| Board, John A. | Duke University (Board, John A.) | FED | NSF |
| D'Mello, Michael | Thinking Machines Corporation (Thinking Machines Corporation) | IND | |
| Heller, Helmut | University of Illinois (Schulten, Klaus) | FED | NIH |
| Humphrey, William | University of Illinois (Schulten, Klaus) | SCCF | |
| Krogh, Michael | University of Illinois (NCSA) | FED | NSF |
| Kufrin, Rick | University of Illinois (NCSA) | FED | NSF |
| Sinha, Amitabh | University of Illinois (Kale, Laxmikant) | FED | NSF |
| Windemuth, Andreas | University of Illinois (Schulten, Klaus) | IND | |

BRTP unit: (T)

NUMBER PUBLISHED –

| | | | | | |
|---|---|---|---|---|---|
| Books: | 2 | Papers: | 32 | Abstracts: | 2 |

NUMBER IN PRESS –

| | | | | | |
|---|---|---|---|---|---|
| Books: | 0 | Papers: | 12 | Abstracts: | 1 |

PUBLISHED:

* D. Barsky, B. Pütz, K. Schulten, and R. L. Magin: "Theory of Compartmentalized Contrast Agents: Improved Contrast for Microscopic MRI", in "Tenth Annual Scientific Meeting and Exhibition, Works in Progress", page 1183. Society of Magnetic Resonance in Medicine, Inc., 1991.

  K. Boehncke, M. Nonella, and K. Schulten: "Molecular Dynamics Investigation of the Interaction Between DNA and Dystamycin", *Biochemistry*, **30**, 5465–5475 (1991).

  E. Erwin, K. Obermayer, and K. Schulten: "Convergence Properties of Self-Organizing Maps", in T. Kohonen, K. Mäkisara, O. Simula, and J. Kangas, Eds., "Proceedings of the ICANN-91, Helsinki", pages 409–414. Elsevier (North Holland) Amsterdam, 1991, [Beckman Institute Technical Report TB-91-06].

* E. Erwin, K. Obermayer, and K. Schulten: "Formation and Variability of Somatotopic Maps with Topological Mismatch", in "Proceedings of the Fourth Conference on Neural Networks", pages 115–126. Indiana University at Fort Wayne, 1992.

* E. Erwin, K. Obermayer, and K. Schulten: "Self-Organizing Maps: Ordering, Convergence Properties and Energy Functions", *Biol. Cybernetics*, **67**(1), 47–55 (1992).

* E. Erwin, K. Obermayer, and K. Schulten: "Self-Organizing Maps: Stationary States, Metastability and Convergence Rate", *Biol. Cybernetics*, **67**(1), 35–45 (1992).

  H. Grubmüller, H. Heller, A. Windemuth, and K. Schulten: "Generalized Verlet Algorithm for Efficient Molecular Dynamics Simulations with Long-Range Interactions", *Molecular Simulation*, **6**(1–3), 121–142 (1991).

  C. Kurrer, B. Nieswand, and K. Schulten: "Dynamics of Synchronous Neural Activity in the Visual Cortex", in T. Kohonen et al., Eds., "Artificial Neural Networks", pages 133–138. Elsevier Publishers, North Holland, Amsterdam, 1991, [Beckman Institute Technical Report TB-91-08].

C. Kurrer, B. Nieswand, and K. Schulten: "A Model for Synchronous Activity in the Visual Cortex", in A. Babloyantz, Ed., "Self-Organization, Emergent Properties, and Learning", Volume 260 of *NATO ASI Series B*, pages 81–85, New York, 1991. Plenum Press.

C. Kurrer and K. Schulten: "Effect of Noise and Perturbations on Limit Cycle Systems", *Physica D*, **50**, 311–320 (1991).

C. Kurrer and K. Schulten: "Propagation of Chemical Waves in Discrete Excitable Media: Anisotropic and Isotropic Wave Fronts", in A. V. Holden et al., Eds., "Nonlinear Wave Processes in Excitable Media", Volume 244 of *NATO ASI Series B*, pages 489–500, New York, 1991. Plenum Press.

T. Martinetz and K. Schulten: "Neural Gas Network for Vector Quantization and Learning of Unknown Topologies", *Neural Comp.*, submitted.

T. Martinetz and K. Schulten: "A 'Neural Gas' Network Learns Topologies", in T. Kohonen, K. Mäkisara, O. Simula, and J. Kangas, Eds., "Artificial Neural Networks", pages 397–402. Elsevier Science Publishers (North Holland) Amsterdam, 1991, [Beckman Institute Technical Report TB-91-05].

T. Martinetz, J. Walter, and K. Schulten: "Neural Network with Hebbian-like Adaptation Rules Learning Control of a PUMA Robot", *NIPS*, (1991), submitted.

C. Niedermeier and K. Schulten: "Molecular Dynamics Simulations in Heterogenous Dielectrica and Debye-Hückel Media — Application to the Protein Bovine Pancreatic Trypsin Inhibitor", *Molecular Simulation*, **8** (1992), issue 6.

* M. Nonella and K. Schulten: "Molecular Dynamics Simulation of Electron Transfer in Proteins — Theory and Application to $Q_A \rightarrow Q_B$ Transfer in the Photosynthetic Reaction Center", *J. Phys. Chem.*, **95**, 2059–2067 (1991).

* M. Nonella, A. Windemuth, and K. Schulten: "Structure of Bacteriorhodopsin and *in situ* Isomerization of Retinal: A Molecular Dynamics Study", *J. Photochem. Photobiol. B*, **54**, 937–948 (1991), [Beckman Institute Technical Report TB-91-03].

K. Obermayer, H. Ritter, and K. Schulten: "Development and Spatial Structure of Cortical Feature Maps: A Model Study", in D.Touretzky and R.Lippman, Eds., "Advances in Neural Information Processing Systems 3", pages 11–17. Morgan Kaufmann Publ. San Mateo CA, 1991.

K. Obermayer, H. Ritter, and K. Schulten: "A Model for the Development of the Spatial Structure of Retinotopic Maps and Orientation Columns", in A. Baskin

and J. Mittenthal, Eds., "The Principles of Organization in Organisms – Santa Fe Institute Studies in the Sciences of Complexity", Volume 12. Addison-Wesley, 1991.

* B. Pütz, D. Barsky, and K. Schulten: "Edge Enhancement by Diffusion: Microscopic Magnetic Resonance Imaging of an Ultra-Thin Glass Capillary", *Chem. Phys. Letters*, **183**, 391–396 (1991), [Beckman Institute Technical Report TB-91-02].

* B. Pütz, D. Barsky, and K. Schulten: "Edge Enhancement in Microscopic MRI", in "Tenth Annual Scientific Meeting and Exhibition, Works in Progress", page 1252. Society of Magnetic Resonance in Medicine, Inc., 1991.

* B. Pütz, D. Barsky, and K. Schulten: "Edge Enhancement by Diffusion in Microscopic Magnetic Resonance Imaging", *J. Mag. Res.*, **97**, 27–53 (1992), [Beckman Institute Technical Report TB-91-01].

* H. Ritter, T. Martinetz, and K. Schulten: "Neural Computation and Self-Organizing Maps: An Introduction". Addison-Wesley, New York, 1991.

* H. Ritter, T. Martinetz, and K. Schulten: "Textbook: Neural Computation and Self-Organizing Maps: An Introduction". revised English edition Addison-Wesley, New York, 1991.

H. Ritter, K. Obermayer, K. Schulten, and J. Rubner: "Self-Organizing Maps and Adaptive Filters", in J. van Hemmen, E. Domany, and K. Schulten, Eds., "Physics of Neural Networks", pages 279–304. Springer, New York, 1991.

* K. Schulten and M. Tesch: "Coupling of Bulk Atomic Motion to Electron Transfer: Molecular Dynamics and Stochastic Quantum Mechanics Study of Photosynthetic Reaction Centers", *(Chemical Physics)*, (submitted to special issue on protein dynamics).

* K. Schulten: "Computational Biology on Massively Parallel Machines", in "Proceedings of the International Conference on Parallel Computation, Salzburg, Austria". Springer, New York, 1991, in press.

* K. Schulten and M. Tesch: "Coupling of Protein Motion to Electron Transfer: Molecular Dynamics and Stochastic Quantum Mechanics Study of Photosynthetic Reaction Centers", *Chem. Phys.*, **158**, 421–446 (1991), [Beckman Institute Technical Report TB-91-15].

M. A. Shifman, A. Windemuth, K. Schulten, and P. L. Miller: "Molecular Dynamics Simulation on a Network of Workstations Using a Machine-Independent Parallel Programming Language", *Computers and Biomedical Research*, **25**, 186–180 (1992).

* H. Treutlein, K. Schulten, J. Deisenhofer, H. Michel, A. Brünger, and M. Karplus: "Chromophore-Protein Interactions and the Function of the Photosynthetic Reaction Center: A Molecular Dynamics Study", *Proc. Natl. Acad. Sci. USA*, **89**, 75–79 (1991), [Beckman Institute Technical Report TB-91-10].

* B. Walberer and K. Schulten: "WATER — a Program for the Implicit Inclusion of Water in Molecular Dynamics Simulations of Proteins", Technical report, Beckman Institute, 1991, in preparation; [Beckman Institute Technical Report TB-91-17].

  J. Walter, T. Martinetz, and K. Schulten: "Industrial Robot Learns Visuo-Motor Coordination by Means of 'Neural Gas' Network", *Proceedings of the International Conference on Artificial Neural Networks, Helsinki*, 357–364 (1991), in press, [Beckman Institute Technical Report TB-91-07].

  J. Walter and K. Schulten: "Implementation of Self-Organizing Neural Networks for Visuo-Motor Control of an Industrial Robot", *IEEE Transactions on Neural Networks*, submitted, [Beckman Institute Technical Report TB-91-21].

  A. Windemuth and K. Schulten: "Molecular Dynamics on the Connection Machine", *Molecular Simulation*, **5**, 353–361 (1991).

  A. Windemuth and K. Schulten: "Stochastic Dynamics Simulation for Macromolecules", [Beckman Institute Technical Report TB-91-19], 1991.

* 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.*, submitted; [Beckman Institue Technical Report TB-91-16].

In Press:

* D. Barsky, B. Pütz, and K. Schulten: "Exploiting Biexponential Relaxation to Detect Capillaries in MRI", *Mag. Res. in Medicine*, submitted; [Beckman Institute Technical Report TB-91-23].

* D. Barsky, B. Pütz, K. Schulten, J. Schoeniger, S. Blackband, and E. W. Hsu: "Diffusional Edge Enhancement Observed by NMR in Thin Glass Capillaries", *Chem. Phys. Lett.*, submitted.

* D. Barsky, B. Pütz, K. Schulten, J. S. Schoeniger, E. W. Hsu, and S. J. Blackband: "Diffusional Edge Enhancement Observed by NMR Microscopy in Thin Glass Capillaries", in "Eleventh Annual Scientific Meeting and Exhibition, Works in Progress". Society of Magnetic Resonance in Medicine, Inc., 1992, (in press).

W. Bauer and K. Schulten: "Theory of Contrast Enhancing Agents in NMR Tomography - The Role of Transport Processes", *Mag. Res. in Medicine*, submitted.

S. Berkovich, P. Dalger, T. Hesselroth, T. Martinetz, B. Noél, J. Walter, and K. Schulten: "Vector Quantization Algorithm for Time Series Prediction and Visuo-Motor Control of Robots", *Informatikberichte*, **291**, 443–447 (1991).

M. Grossjean, M. S. Grossjean, K. Schulten, and P. Tavan: "A Semistochastic Approach to Many Electron Systems", *J. Chem. Phys.*, submitted.

* H. Heller, M. Schaefer, and K. Schulten: "Construction, Molecular Dynamics Simulation and Analysis of a Lipid Bilayer", *Biochemistry*, (1992), in preparation.

* H. Heller and K. Schulten: "Parallel Distributed Computing for Molecular Dynamics: Simulation of Large Heterogeneous Systems on a Systolic Ring of Transputers", in S. I. Sayegh, Ed., "Proceedings of the Fifth Conference on Neural Networks and Parallel Distributed Processing". Department of Physics, Indiana University–Purdue University at Fort Wayne, Indiana, U.S.A., Indiana University–Purdue University at Fort Wayne, 1992, [Beckman Institute Technical Report UIUC-BI-TB-92-09].

* H. Heller and K. Schulten: "Parallel Distributed Computing for Molecular Dynamics: Simulation of Large Heterogeneous Systems on a Systolic Ring of Transputers", *Chemical Design Automation News (CDA News)*, **7**(8), 11–22 (1992), This publication is a reprint of [67].

T. Martinetz and K. Schulten: "A Neural Network for Robot Control: Cooperation Between Neurons Enhances Learning", *Computers and Elect. Engr.*, submitted to special issue on 'Neural Networks: Theory and Applications in Robotics and Manufacturing'.

K. Obermayer, K. Schulten, and G. Blasdel: "A Comparison Between a Neural Network Model for the Formation of Brain Maps and Experimental Data", in D. S. Touretzky and R. Lippman, Eds., "Advances in Neural Information Processing Systems 4". Morgan Kaufmann Publishers, 1992, in press; [Beckman Institute Technical Report TB-92-01].

* A. Sinha, H. Heller, and K. Schulten: "Performance Analysis of a Parallel Molecular Dynamics Program", *Comput. Phys. Commun.*, (1992), submitted, [Beckman Institute Technical Report UIUC-BI-TB-92-13].

* F. Zhou, A. Windemuth, and K. Schulten: "Molecular Dynamics Investigation of the Proton Pump Cycle of Bacteriorhodopsin", *Biochemistry*, (1992), submitted, [Beckman Institute Technical Report TB-92-02].

BRTP unit: (C)

NUMBER PUBLISHED –
Books: 0 Papers: 2 Abstracts: 0

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

PUBLISHED:

K. Obermayer, G. G. Blasdel, and K. Schulten: "A Neural Network Model for the Formation and for Spatial Structure of Retinotopic Maps, Orientation- and Ocular dominance Columns", in T. Kohonen, Ed., "Artificial Neural Networks", pages 505–511. Elsevier Science Publishers (North Holland) Amsterdam, 1991, [Beckman Institute Technical Report TB-91-09].

* K. Obermayer, G. G. Blasdel, and K. Schulten: "Statistical Mechanical Analysis of Self-Organization and Pattern Formation during the Development of Visual Maps", *Phys. Rev. A*, **45**(10), 7568–7589 (1992).

IN PRESS:

* J. A. Board, Jr., J. W. Causey, J. F. Leathrum, Jr., A. Windemuth, and K. Schulten: "Accelerated Molecular Dynamics Simulation with the Parallel Fast Multipole Algorithm", in press, 1992.

BRTP unit: (D)

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

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

Published:

* B. Banko and H. Heller: "User Manual for EGO", Theoretical Biophysics Group at the University of Illinois at Urbana-Champaign, Physics Department, Beckman Institute, 405 N. Mathews Ave., Urbana, IL 61801, U.S.A., 1991, [Beckman Institute Technical Report UIUC-BI-TB-92-07].

In Press:

Not applicable

# Dissemination and Training

The Resource currently employs several methods for dissemination of information and programs, 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).

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).

**Outside Lectures**

The PI presented the following invited lectures:

- Parallel Computing in Chemical Physics Workshop, Argonnne National Laboratory, Argonne, IL, July 17-19, 1991: *Concurrent Biological Computing: Concepts, Results, Opportunities*
- American Crystallographic Association Annual Meeting, University of Toledo, Toledo, Ohio, July 21-26, 1991: *Molecular Dynamics on Parallel Computers*
- Biosym Technologies, Inc. (Invited Speaker), San Diego, CA, September 5-6, 1991: *Molecular Dynamics on Parallel Computers*
- First International Conference of the Austrian Center for Parallel Computation, University of Vienna, Austria, September 30 - October 2, 1991: *Computational Neural Science on Massively Parallel Machines*
- Board of Visitors Meeting, Champaign, IL, October 15-16, 1991: *Modelling: How does one prepare for research at the intersection of life science, physical science, and algorithm generation?*
- 4th International GI Congress, Munich, Germany, October 23-24, 1991: *Modelling the Formation of Visual Maps in the Striate Cortex: Biological, Computational and Mathematical Challenges*
- Workshop on Advanced Computer Visualization and Simulation, Washington, DC, November 5-6, 1991: *Computational Biology on High Performance Computers and Graphics Engines: Methods, Results, Opportunities*

- Lawrence Livermore National Laboratory, Livermore, CA, December 17-19, 1991: *Molecular Dynamics on Parallel Computers* and *Computational Neural Science on Parallel Computers*

- Workshop on High Performance Computing and Grand Challenges in Structural Biology, Florida State University, January 24-27, 1992: *Molecular Dynamics on Parallel Computers*

- AAA Science Symposium, Chicago, IL, February 7-11, 1992: *Computational Neural Science: Reception, Presentation, Cognition and Response in Vision*

- Pharmaceutical Chemistry 221 Seminar, University of California, School of Pharmacy, San Francisco, CA, February 20-23, 1992: *Molecular Dynamics on Parallel Computers*

- University of North Carolina - Concert, March 1-3, 1992: *Fast Molecular Dynamics on Parallel Computers*

- Fast Processes in Protein Folding Dynamics, San Juan, Puerto Rico, March 19-21, 1992: *Computational Challenges in Structural Biology*

- APS Symposium on Computational Biological Physics, Indianapolis, IN, March 16-20, 1992: *Computational Biology on Massively Parallel Machines*

- 2nd Symposium on Molecular Reaction Dynamics in Condensed Matter, Newport, California, April 2-4, 1992: *Molecular Reaction Dynamics in Proteins*

- Workshop Photosynthesis, Cadarache, France, May 10-15, 1992: *Theoretical Modelling on Spectra; Calculations*

- 25th Jerusalem Symnposium on Quantum Biology, May 17-21, 1992: *Molecular Dynamics Simulation of Membranes and Membrane Proteins*

- Computer Vision Conference, Champaign, IL, June 16-18, 1992: *Biological Vision and Visuo-Motor Control*

The PI during the past year also participated in the following committee meetings:

- National Research Council Scope Meeting, September 19-20, 1991

- National Science Foundation Conference, Program Advisory Panel for Advanced Scientific Computing, Washington, DC, December 8-10, 1991

- Workshop on the Role of the NSF Supercomputer Centers in the National High-Performance Computing Effort, Houston, Texas, March 6-8, 1992

- Science in 100 T Workshop, Leuven, Belgium, May 15-17, 1992
- NIH Study Session, June, 1992

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

- Computational Neuroscience Summer School, Marine Biological Lab, Woodshole, MA (Obermayer, August 1991)
- SMRM 10th Annual Meeting, San Francisco, CA (Barsky, August 1991)
- 4th Annual Cell and Molecular Biology Molecular Biophysics Research Symposium, Urbana, IL (posters, September 1991)
- Titisee Conference, Titisee, Germany (Obermayer, October 1991)
- CECAM 92 Workshop on "Molecular Dynamics Simulations of Proteins in Lipid Membranes"(Heller, January 1992)
- Neural Networks for Computing, Utah (Obermayer, March 1992)
- 5th Conference on Neural Networks and Parallel Distributed Processing, Fort Wayne, IN (Heller, April 1992)
- Grenoble, CENG (Heller, April 1992)
- Groningen (Heller, April 1992)
- Congres Satellite Du Congres Europeen de Mathematiques, Paris, France (Obermayer, July 1992)

**Resource Seminar**

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

- Dr. Martin Gerhardt, University of Bielefeld, Germany, July 1991
- Dr. E.I. Ohmine, Institute of Molecular Science, Okasaki, Japan, August 1991
- Dr. Klaus Buchner, Technical University of Munich, Germany, August 1991
- Dr. Raima Larter, Indiana University, September 1991
- Dr. John P. Phillips, University of Indiana, November 1991

- Dr. Jude Shavlik, University of Wisconsin, December 1991
- Dr. Uri Dinur, Ben-Gurion University of the Negev, Israel, February 1992
- Dr. John Board, Duke University, February 1992
- Dr. Zhaoping Li, Princeton University, March 1992
- Dr. Tim Mattson, Yale University, April 1992
- Dr. David Micha, University of Florida, June 1992

# Bibliography


[1] L. Greengard and V. Rohklin: "A Fast Algorithm for Particle Simulation", *J. Comp. Phys.*, **73**, 325–348 (1987).

[2] L. Greengard: "The Rapid Evaluation of Potential Fields in Particle Systems". MIT Press, Cambridge, 1988.

[3] A. Windemuth and K. Schulten: "Molecular Dynamics on the Connection Machine", *Molecular Simulation*, **5**, 353–361 (1991).

[4] N. Carriero and D. Gelernter: "How to Write Parallel Programs: A Guide to the Perplexed", *ACM Computing Surveys*, **21**(3), 323–357 (1989).

[5] N. Carriero and D. Gelernter: "Linda in Context", *Comm. ACM*, **(32,4)**, 444–458 (1989).

[6] R. D. Bjornson: "Linda on Distributed Memory Multiprocessors", PhD thesis, Yale University, Dept. of Comp. Sci., New Haven, CT, 1991.

[7] T. G. Mattson, R. Bjornson, and D. Kaminsky: "Beyond Parallelism to Coordination", in "Proceedings of the Sun Users Group", San Jose, CA, 1991.

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