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Symposium Overview
Minnesota Conference on Supercomputing in Biology: Proteins, Nucleic Acids, and Water

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This was the first academically organized conference dealing exclusively with biological applications of supercomputers. The symposium was organized to explore in a systematic way the current state of the art in application of large scale computation to problems in physical biochemistry. The conference was held September 13–16, 1987 on the campus of the University of Minnesota in Minneapolis, Minnesota. Primary support was provided by the Minnesota Supercomputer Institute; other support came from other divisions of the University and from several corporations. Total attendance was over 140, including 24 speakers and session chairpersons.

The tone of the meeting was set from the outset and reinforced by the session entitled *Futures in Biomolecular Computation*. This tone consisted of a challenge to consider how future generations of computers might allow the exploration of systems of unprecedented complexity with unprecedented levels of analysis. Most of the presentations dealt exclusively with biophysical issues related to the problems being studied. However, the panel sessions, which involved the speakers and chairpersons after each group of presentations, encouraged discussions of computational methodology and controversial aspects of the research. The emphasis on biophysics and the tone of future directions combined to make the conference an exciting examination of future developments in protein and nucleic acid biochemistry.

The use of supercomputers in the design of crystallographic and spectroscopic studies of molecular structure and in analysis of data from those studies was addressed in the first session of the meeting. This session dealt with structure determination using physical probes such as X-ray diffraction and nuclear magnetic resonance (NMR). In X-ray diffraction studies, both data analysis and structure refinement for large molecular systems, including viruses, currently require large scale computation. The future evolution of these and other experimental approaches to biophys-

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ics (e.g., electron paramagnetic resonance and fluorescence studies) will involve increased use of supercomputers; for example, crystallographers are adopting molecular dynamics simulations to pose functional questions about their structural data. This hybrid approach was referred to several times throughout the meeting.

In the case of protein structure prediction, heated discussion developed concerning the ease with which one can predict three-dimensional structure from primary sequence information alone. Although this long-standing debate was not resolved at the conference, consensus was reached that several potentially valid procedures exist, including massive energy minimization of partially constrained structures, assembly from known oligopeptide structures or the application of artificial intelligence (AI) and expert system techniques. This lack of unanimity indicates that unrestricted access to supercomputers may be insufficient to predict protein tertiary structure and that further development of methodologies and establishment of confidence limits will be required for agreeable solutions. One possibility is the development of expert systems 'trained' to apply the rules of protein folding to primary sequences of proteins with unknown structure.

Molecular simulations span the range from quantum mechanical studies of electrons passing among tens of atoms to Brownian dynamics simulations of assemblies of tens of thousands of atoms. Molecular dynamics simulations account for much of the growth in use of supercomputers in physical biochemistry over the past ten years [1]. Whereas advances in available computer power have driven some of the developments in the field, future advances will require more creative use of available resources. The use of short cuts, such as the mutation of one bound ligand to another, allows rapid quantitative comparison of the binding constants. Such an analysis applied to point mutation of an amino acid in protein with known structure may yield predicted structures with high confidence. Simulated annealing, which provides a means for allowing protein structures to pass through 'impossible' transitions involving bond breaking and reformation, for example, may also yield useful predictions of tertiary structure. At the other end of the spectrum, looking at molecular systems in more detail using quantum mechanics may allow prediction of electronic behavior in a part of the molecule thought to participate directly in function.

Due to the complexity of the problem, the inclusion of long range (> 10 Å) electrostatic effects in molecular dynamics simulations of diffusional encounters requires the use of Brownian dynamics methods. Molecular dynamics simulation of large molecule docking in electron transfer reactions can also suggest molecular details which may be important for effective electron transfer in protein-protein complexes. Consideration of longer range interactions on a larger scale entails the inclusion of more molecules in simulations running hundreds of times longer; the scale of these problems often requires the imposition of further simplifications. For example, some of these studies reduce the clutter of individual water molecules to a continuum of a water-like dielectric using finite difference analysis. Analysis of the diffusional encounter of reaction partners often assumes rigid molecules in simulations designed to give the frequency of successful collisions to estimate the rate constant of the reaction.

The last session touched on several areas not covered during the previous sessions. Subjects included applications of supercomputers to protein and nucleic acids, to sequence analysis, to the simulation of micelle structure and dynamics, and to the development of an expert system for studying and generating the rules governing the structure and functions of proteins. This session brought together ideas from previous sessions and suggested applications for some of the methods addressed in the earlier sessions.

Session on Structure Determination

Large scale computers are used in the analysis of X-ray diffration data and in the refinement of structures of very large molecular systems such as viruses. Several groups are currently investigating detailed structures of virus capsid with potential bound antiviral drugs. Michael Rossmann's group at Purdue conducts studies of picorna viruses, such as rhinovirus; these viruses are named for their small size (*pico*) and their genetic material (*RNA*). John Badger, a research associate working with Rossmann, described studies of these viruses which follow and complement the original determination of their structure by this group [2]. These studies specifically address how potential antiviral agents insert themselves into the viral capsid. Using structures determined in the absence of drug as a starting point, X-ray determination of a new drug-including structure is relatively easy. This allowed Badger and his colleagues to determine virus-drug structures for several members of a family of antiviral agents. The results showed that the drug molecule had inserted itself into pores in the capsid. Unfortunately, no correlation has yet been found between the mode of drug insertion and infectivity. This work is an example of X-ray- and computer-assisted drug design on an unprecedented scale; in the future, structure-activity relationships for several candidate agents can be studied in molecular detail before predictions of efficacy are made.

John Kuriyan described studies conducted in collaboration with Gregory Petsko and Martin Karplus [3]. The studies examined monomeric proteins using X-ray-determined structures as the starting point for molecular dynamics simulations. These methods are important to refine protein structures beyond the information provided by the X-ray diffraction results. For example, structures of residues which are free to rotate at the surface of a large protein cannot be resolved with crystallography; such substructures can be estimated using methods such as simulated annealing. X-ray data is also limited in that it can provide information for individual residues and atoms which presumes isotropic freedom of motion (i.e., within a sphere), while molecular dynamics simulations can examine the consequences of anisotropic motion (i.e., within an elipsoid). Florante Quiocho, a crystallographer and chairman of the session, briefly described his own molecular dynamics extensions to crystallographic studies. He and his student, H. Luecke, are examining the mechanisms of charge stabilization of sulfate ion within a carrier protein; the simulations indicate that charge can be stabilized primarily by hydrogen bonds with peptide units in the protein [4].

Large scale computation similarly facilitates the analysis of data from two dimensional nuclear magnetic resonance (2D NMR) spectroscopy; these studies probe the structure of large molecules in aqueous solution through examination of interactions between protons. Brian Reid discussed his studies of DNA dodecamers in which assignment of the proton resonances allows analysis of helix bending [5]. In addition to chemical shift peaks, whose locations on the diagonal of the 2D spectrum are dependent on the immediate environment of protons, 2D NMR provides off-diagonal peaks, which represent proton-proton interactions over distances of several Ångstrom units. Cross-relaxation intensities plotted over tens of milliseconds reveal faster rates of change for shorter distances and correspondingly longer rates for longer distances; the time constant of these changes is related to the interproton distance raised to the sixth power, limiting the range of interaction studies. In DNA oligomers, longer range interactions can be assigned to protons on neighboring turns of the double helix.

Like many of the computations in the experimental branch of the field, Reid's calculations use conventional-scale host computers (i.e., VAX 11/780) and medium scale vector processors (i.e.,

Convex C-1) doing energy calculations coded in special-purpose programs. The panel of experimental investigators (the other sessions were more theoretical) agreed that future developments in their studies relied more on developments in instruments (e.g., larger magnets in NMR for better resolution, more powerful X-ray sources and higher resolution X-ray detectors) than on increases in computer power. In other words, current technology in array processors suffices because computation is not the limiting factor in their research.

Session on Structure Prediction

The Structure Prediction session proved to be the most controversial of the meeting. Cyrus Levinthal introduced the session by describing the protein folding problem, which has interested him for the last 25 years [6]. DNA sequencing is proceding far more rapidly than three-dimensional (3D) structures of proteins can be determined by physical means. As homologies are discovered between proteins and within families of proteins, the utility of deriving predicted structures of proteins from known structures of related proteins becomes attractive. Site directed mutagenesis allows creation of variants of proteins with altered functional characteristics; structure prediction for a variant allowing hypotheses concerning its function to be proposed before the variant is tested biochemically for function enhances the value of the experiments. The availability of more powerful computers makes rigorous molecular dynamics and energy minimization of protein structure possible at an unprecedented scale. Levinthal described a special purpose attached processor which he and Richard Fine designed at Columbia and which is being constructed in collaboration with the Brookhaven National Laboratory. This processor, called FASTRUN, is optimized for rapid pairwise energy and force calculations which consume most of the computational time in molecular dynamics or energy minimization calculations. The system is expected to be available for production calculations in 1988, but of course only for molecular mechanics calculations.

Richard Fine, who works with Levinthal at Columbia University, described an application for such large scale calculations to the prediction of the structure of a hypervariable region of an antibody molecule. In this case, the known structure of the invariant part of the molecule can constrain the boundaries of the unknown structure of the variable region. Fine has predicted a library of possible folding patterns based on simple torsional minimization; he then uses intensive energy minimization calculations to select those structures with the lowest energies. The result of these calculations is a reduced set of possible configurations for the variable region of this antibody.

Harold Scheraga described a conceptually simpler approach to the protein folding problem which relies on torsional minimization and build-up of large proteins from smaller peptides [7]. This procedure, embodied in a widely available program called ECEPP, assumes that short range molecular interactions are dominant. Basically knowledge of all possible dihedral angles for the 20 amino acids is put in a table which is searched for a predicted structure for a peptide and then a series of peptides. Scheraga made an analogy indicating that this procedure is similar to folding that takes place in normal synthesis of proteins in cells. The relative simplicity of this approach contrasted with the exhaustive calculations proposed by Levinthal and Fine. This disagreement led to a discussion during the panel session which followed. Levinthal's view is that folding models (e.g., the Fasman rules [8] or Scheraga's procedure) that do not deal with interactions between sections of the peptide which are not adjacent to each other along the amino acid sequence

(i.e., tertiary interactions) lead to unrealistic predictions; such models only predict the possible nucleation regions for the protein, not its final conformation.

Fred Cohen discussed some novel approaches to the folding problem which incorporate AI techniques [9]. Cohen discussed the numerology of possible structures for moderately sized proteins, such as myoglobin, when one knows the α-helices of which it is composed. From 10 000 possibilities, he reduces the problem to about 20 possible ways to arrange the six α-helices, each with 3–5 Å resolution. This range of possible structures was reduced to two possible structures by constraining the two histidine residues to bind with the heme. Selecting the correct structure and ascribing a level of confidence, however, awaits future developments of the technique.

Session on Dynamics and Recognition

The session on Dynamics and Recognition focused on applications of molecular dynamics simulations to calculate thermodynamic and structural properties of biological molecules and their complexes. Andrew McCammon introduced the session with a brief review of the history of molecular dynamics simulations in biology. The first such simulation was done ten years ago. Although the calculation made use of one of the supercomputers of its day (an IBM 360/91E), it was only possible to simulate the atomic motion of a small protein (58 residues) in vacuo for a period of a few picoseconds. Current supercomputers are roughly 100 times more powerful, so that more detailed and realistic models can be considered. One recent calculation involved the enzyme trypsin in a bath of nearly 5000 water molecules; the CPU time (on a Cyber 205) for a picosecond of simulation was comparable to that for the small protein in vacuo studied ten years ago. There have also been dramatic advances in the theory that underlies computer simulations during the past decade. Together, the advances in computers and theory have made possible the analysis and prediction of biomolecular activity [1].

The first talk in the session, given by Terry Lybrand, illustrated the above points very nicely. Lybrand described a recent theoretical method that has made possible the quantitative prediction of how changes in the composition of ligand or receptor molecules will change the free energy of association of these molecules [10]. In this method, one slowly changes the molecular composition of the molecules in dynamic simulations of both the unbound and complexed states. The free energies for these two (nonphysical) processes are calculated by using simple equations from statistical mechanics, and a thermodynamic argument is used to show that the difference of these two free energy changes is equal to the desired difference in (physical) free energies of binding. Lybrand described a number of applications that are in progress, including calculations of the relative free energies of binding of different antibiotics to DNA, different sugars to the L-arabinose-binding protein, and different drugs to the coat proteins of the human rhinovirus. Although a theoretical advance made these studies possible, the actual calculations still require access to supercomputers in many cases.

Bill Goddard described several projects that also blend state-of-the-art theory and computation. Most of these projects are intended to provide methods to sample large changes in molecular configuration [11]. In one study, simulated annealing (simulating structural fluctuations at high temperature followed by cooling) has been combined with phantom chain steps (in which covalent strands are allowed to pass through each other) to generate folded conformations of large molecules. In another study, detailed simulations of a 10 base pair DNA helix have been analyzed

to obtain elastic parameters that can then be used in simplified models of much larger DNA molecules.

Chung Wong noted that previous simulations of biomolecular systems have always assumed that the motion of the atoms obeyed classical dynamics. Using supercomputers, the Feynman path integral techniques that have been used recently to study quantum dynamics of liquids can be applied to proteins. A quantum dynamic simulation of the atomic motion in cytochrome c was described, as were possible extensions to study electron and proton transfers.

Session on Dynamics and Reactivity

It has long been recognized that electrostatic effects are extremely important in determining reactivity in biological macromolecules, but conventional modeling methods have not been equal to the task of accurately describing electrostatic effects. The session on Dynamics and Reactivity presented results from simulations examining the diffusive encounter of proteins with small substrates and with other proteins, and the speakers gave considerable attention to the problems of accurately treating electrostatic interactions.

Steve Harvey introduced the session with a discussion of the importance of electrostatic effects and a review of how they have been treated in previous simulations using molecular mechanics, molecular dynamics, Brownian dynamics and Monte Carlo [1]. Traditionally, a simple pairwise interaction following Coulomb's law is used, and sometimes a distance-dependent dielectric constant is introduced to crudely mimic solvent effects on electrostatic interactions. With the advent of supercomputers, one can either treat larger problems (bigger molecules; longer time scales), or one can use the additional computer power to model the systems more realistically. Given the importance of electrostatic effects, and considering that the largest errors in existing potential functions are in the electrostatic terms, alternative approaches to handling electrostatics are worth considering.

Barry Honig gave a rigorous review of electrostatics in macromolecular systems and described the approach he, Kim Sharp, and their collaborators have taken [12]. Because proteins and nucleic acids have dielectric constants typical of organic materials (in the range of 2-4), while water has a dielectric constant near 80, electrostatic forces are often treated with a distance-dependent dielectric constant, although that fails to reproduce the forces between charges in the macromolecule and their images in the solvent. The situation is further complicated by the presence of counterions in the solution, a consideration that is especially important for nucleic acids, because of their polyelectrolyte nature. Honig and his collaborators have implemented a finite difference algorithm for numerically solving the Poisson-Boltzmann equation for macromolecules in a solvent of specified dielectric constant and ionic strength. They are using this program in Brownian dynamics simulations and are examining the possibility of incorporating it into molecular mechanics and molecular dynamics simulations.

Kim Sharp then described the application of the algorithm described above in a Brownian dynamics simulation of the encounter of the superoxide anion with the enzyme superoxide dismutase [13]. An analysis of the patterns of electrostatic potential around the enzyme as a function of dielectric constant and ionic strength reveals how it is able to achieve catalysis at a rate quite near to the limit imposed by diffusion, even though the protein and the substrate are both negatively charged. Superoxide dismutase is a copper-zinc enzyme, and the positive charge at the bottom of

the reactive site, arising from the presence of these metal ions, creates a lobe of attractive electrostatic potential that reaches out into the solvent; the dependence of reaction rate on ionic strength can be understood by the dependence of the potential surface on ionic strength. Brownian dynamics simulations of the motion of the superoxide anion at various ionic strengths give good agreement with the experimental reaction rates.

Moving up to a more complex system, Scott Northrup described his research on the diffusional encounter between two macromolecules, cytochrome c and cytochrome c peroxidase [14]. He, too, has implemented a program to solve the Poisson-Boltzmann equation using the finite difference method. This algorithm has been used to calculate the electrostatic potential around the larger protein, cytochrome c peroxidase. The encounter between the two molecules is then simulated using a new Brownian dynamics algorithm that treats both the translational and rotational diffusion of the smaller molecule, cytochrome c, in the electrostatic field of the larger protein. Several results were reported. The method is able to reproduce the dependence of the association rate on ionic strength in the physiological range. The results also strongly suggest that, for electron transfer to occur, the hemes in the two proteins must be at least partially aligned. Interestingly there are two distinct encounter geometries, with the cytochrome c in either of two docking positions on different parts of the surface of the peroxidase. For both of these kinds of complexes, a large number of different relative orientations were observed.

In the final talk, Ray Salemme described a molecular dynamics simulation that explores the details of the interactions between two proteins after initial docking [15]. A trial docking complex was formed with the crystallographic models of cytochrome c and cytochrome b5; this was done manually using computer graphics, followed by energy minimization. Patterns of charged groups on the molecular surfaces were examined, and the trial complex attempted to optimize electrostatic interactions while achieving a reasonably coplanar geometry for the heme groups in the two molecules. This trial structure was then refined by simulated annealing with molecular dynamics. The two molecules were observed to move closer together during the dynamics simulation than they had during energy minimization, because the simulated thermal motions allow the two surfaces to adjust to one another. A video movie of the simulation reveals substantial flexibility in the association complex, with a wide range of conformations and interheme geometries. A particularly interesting result of the simulation was the spontaneous motion of Phe-82 of cytochrome c into a position that bridges the two hemes. This is particularly striking in view of the fact that Phe-82 is a highly conserved residue, and in light of the recent experimental observation that point mutations at that position can have profound effects on the electron transfer rate [16].

Session on Medical and Industrial Applications

At present, applications of supercomputers to problems in medicine and in the pharmaceutical-biotechnology industry lag behind those in chemistry, physics, and engineering. The usefulness of supercomputing in the former areas is, however, becoming clear, driven to a large extent by the need to understand the molecular complexity of biological systems in order to design new drugs and bioactive agents more effectively. As most experiments do not provide an appropriate level of molecular detail directly, the ability to analyze, model, or simulate the properties of biomolecular systems by 'numerical experiments' on supercomputers has provided a means for, at least partially, dealing with this difficulty. Certainly, the continued development and refinement of new meth-

odologies such as thermodynamical-cycle perturbation theory and distance geometry will have a major impact on our understanding of biomolecular structure and interactions.

In addition to the more traditional applications of supercomputers such as have been described in a number of earlier presentations in this Symposium, several other less 'traditional' applications are also gaining in importance both within industry and without. The final session focused on three such applications which exploit the power of supercomputers: (1) management and analysis of polynucleotide and protein sequence data; (2) structural features of micelles and membranes; and (3) development of an AI-based expert system design to help 'discover' and apply the 'rules' governing biomolecular structure and function.

The first presentation was given by Jacob Maizel, Chief of the Laboratory of Mathematical Biology at the National Cancer Institute. Maizel gave a brief introduction outlining the general organizational features of the NCI's new Advanced Scientific Computing Laboratory. Currently, the Laboratory is designed to support research in a wide range of areas including crystallography, molecular dynamics, image analysis, and sequence analysis. The discussion centered primarily on the latter area, and included a number of examples based on comparisons among gene sequences and the prediction of RNA secondary structure [17]. For example, sequence comparisons can provide information on subtle relationships which may be indicative of functional similarities between genes and their products, information which may be essential if we are to understand the complex interactions of macromolecules with normal and abnormal cells. The use of supercomputers in such studies is necessitated by the complexity of the information and by the pace with which new sequence information is being added: for example, approximately three million bases are added yearly to the more than ten million bases already stored in the GenBank database, and the rate of new entries is increasing rapidly. When sequencing of the human genome begins in earnest, the amount of sequence information will be staggering, reaching on the order of ten billion bases. Managing and analyzing this amount of sequence information will not be possible on anything but a supercomputer.

The second presentation was given by John Wendolowski, Research Scientist at the E.I. duPont de Nemours Experimental Station [15]. Wendolowski's talk focused on the application of molecular dynamics methods to the study of micelle structure and properties. To date very few theoretical studies of membranes or micelles have been carried out, especially at the level of 'molecular resolution' described by Wendolowski. The fact that a growing body of experimental data now suggests that membranes play manifold roles in the binding of ligands such as hormones to many membrane bound proteins, places added significance on theoretical studies in this area. In addition, such studies provide a basis for sharpening our molecular models of membrane and micelle structure and properties. A number of interesting 'dynamic' phenomena were described which take place even in the 'short-time' regime, that is in simulations lasting less than 50 ps. Of particular interest was the occasional movement of some of the hydrocarbon 'tails' of the lipid molecules out of their normal apolar environments into the interface region containing the polar lipid 'head groups' and the surrounding aqueous environment. Preliminary structural studies of micelle-phospholipase A_2*(PLA_2) complexes indicated significant structural complementarity and a favorable 'electrostatic environment' between the convex outer surface of the micelle and the concave inter surface of the PLA_2 molecule. This finding coupled with information obtained from the molecular dynamics simulations may provide an important clue as to the mechanism for PLA_2 catalysis of ester bond hydrolysis. Although Wendolowski indicated that the latter results were only

very preliminary, they nonetheless showed the power of molecular modeling and simulation methods to provide a more detailed 'molecular picture' than was possible before the advent of such large-scale computational methods.

The final presentation was given by Michael Liebman, Associate Professor of Biophysics in the Department of Physiology and Biophysics at the Mt. Siani School of Medicine. In his talk, with the intriguing title 'Molecular Modeling: An Adult Game in Search of Natural Rules by Use of Artificial Intelligence', Liebman discussed the importance of determining the 'rules' which govern the structure and function of biologically important macromolecules [18]. Although considerable data has been gathered on these systems through numerous experimental and theoretical studies, it has not as yet provided us with a rule base from which we can reason about structure and function. Moreover, there does not exist an 'expert' who can reliably predict structure and biological activity, and hence development of a 'traditional' expert system is not possible at present. Liebman's work is directed towards the generation of such an expert system through development of a computer environment with suitable tools for gathering observations from which rules can be derived and verified. A number of methods for analyzing structural data were presented including a novel method which makes use of speech recognition techniques. The method is based on linear distance plots (LDPs) and difference LDPs derived from the three-dimensional structure of proteins. These plots resemble sonograms obtained from human speech, and can be interpreted in terms 'phonemes' derived from analyses of protein substructures. He also discussed a number of applications of two-dimensional 'matrix plots' of intermonomer distances, electrostatics, and energetics to the analysis of protein structure and properties using pattern recognition, dynamic programming, and interactive computer graphics. A number of examples of molecular design and analysis were presented which illustrated the use of the expert system. An important advantage of Liebman's system is the fact that it can modify its rule base in response to new information which cannot be interpreted within its current rule base — thus showing a form, albeit primitive, of learning behavior.

Conclusions

On Tuesday evening of the Conference, Cray Research sponsored a reception in the new Minnesota Supercomputer Center building. This building houses the Minnesota Supercomputer Institute, which was the major sponsor of the conference, and three supercomputers, two Cray-2 and one Cyber 205, operated by the Minnesota Supercomputer Center Inc. This reception encouraged open discussions of future directions in the field of computational physical biochemistry among the over 100 academic and industrial participants. There was a clear sense of optimism that the possible developments over the next decade are extensive; Andrew McCammon observed that the future promises excitement in the form of unexpected developments. The feeling of most of those present was that, exciting as the pace of supercomputer development is, raw computer power will not be solely responsible for future advances in biomolecular simulations. Clever innovations and careful analyses will yield new approaches that we cannot predict at the present time. It is the search for these innovations that excited the participants in the conference most.

Overall, the meeting focused on two themes which have not often been combined previously. There have been many meetings examining the use of supercomputers in science. There have been many meetings on the biophysics of proteins and nucleic acids. This meeting simultaneously con-

sidered macromolecular biophysics and large scale computation. The majority of speakers at this conference were biophysicists and therefore dealt mostly with the biophysical aspects of their problems. Nonetheless, each speaker discussed his computational approaches to various levels of detail. About half of the speakers used large scale general purpose supercomputers while half performed most of their computations on smaller vector processors. Several of the speakers were directly involved in coding their own problems, while others left the details of software and hardware to specialists. Few, however, are sceptical of the utility of some form of large scale computation in this field. By contrast, in other areas of biological science (image processing and physiological simulation, for example) application of computers to biological problems are not universally welcomed. The difference between biophysics and these other areas seems to be the proximity of a physical starting point for simulation. Equations such as Newton's laws of motion can be easily and justifiably applied to simulations of atomic motion, whereas statistical analysis of images and metaphorical treatment of a physiological system seem distant from the laws of nature.

Given this background, molecular dynamics simulations are well accepted in the field of biophysics. Consequently, computer applications in biophysics have flourished over the past ten years to a degree closely matching the capabilities of the most powerful general purpose computers. This trend shown no signs of abatement, and in fact the accelerating pace of application raised concerns about appropriateness of use, commonality of code and applicability of algorithms. A fundamental question which remained unanswered after the conference was whether investigators should use the available 'canned' programs or enlist the aid of graduate students and programmers in creation of special purpose code. The advantages of standard programs include transportability of input and output data among investigators and prior removal of errors from the programs. The advantages of special purpose code include efficiency of execution and applicability to a particular type of problem. About half of the speakers used programs designed especially for their approach and their problem. The other half of the speakers used various derivatives of the widely available programs, GROMOS, CHARMM and AMBER, for molecular dynamics and energy minimization. All the speakers agreed that caution is necessary in the application of these general purpose programs to particular simulation or minimization problems. The almost deceptive simplicity of these programs makes their misapplication by inexperienced investigators a real possibility.

The conclusion of this meeting held an air of optimism, and the conclusion of this overview should reflect that optimism. The sometimes strongly expressed differences of opinion underscored the presence in the field of several complementary approaches to the common goal of mechanistic explanations for biomolecular interactions. And complementarity within the field is perhaps the most important summary one can apply to this meeting. Experimental approaches test the validity of predictions and seed the simulation of molecular dynamics. The results of the simulations in turn beg the development of new theoretical approaches to electronic, interatomic and intermolecular interactions. The field is thriving and will continue to develop in this atmosphere of complementarity.

REFERENCES

1 McCammon, J.A. and Harvey, S.C., Dynamics of Proteins and Nucleic Acids, Cambridge, London, 1987.

2 Smith, T.J., Kremer, M.J., Luo, M., Vriend, G., Arnold, E., Kramer, G., Rossmann, M.G., McKinlay, M.A., Diana, G.D. and Otto, M.J., Science, 233 (1986) 1286–1293.

3 Kuriyan, J., Wilz, S., Karplus, M. and Petsko, G.A., J. Mol. Biol., 192 (1986) 133–154.
4 Quiocho, F.A., Sack, J.S. and Vyas, N.K., Nature, 329 (1987) 561–564.
5 Kintanar, A., Klevit, R.E. and Reid, B.R., Nucleic Acids Res., 15 (1987) 5845–5862.
6 Levinthal, C., Scientific American, 214 (1966) 42–52.
7 Scheraga, H.A. and Paine, G.H., Ann. N.Y.Acad. Sci., 482 (1986) 60–68.
8 Chou, P. and Fasman, G.D., Biochemistry, 13 (1974) 222–245.
9 Cohen, F.E., Abarbanel, R.M., Kuntz, I.D. and Fletterick, R.J., Biochemistry, 25 (1986) 266–75.
10 McCammon, J.A., Karim, O.A., Lybrand, T.P. and Wong, C.F., Ann. N.Y. Acad. Sci., 482 (1986) 210–221.
11 Goddard III, W.A. and Olafson, B.D., Ann. N.Y.Acad. Sci., 367 (1981) 419–433.
12 Klapper, I., Hagstrom, E., Fine, R., Sharp, K. and Honig, B., Proteins: Structure, Function and Genetics, 1 (1986) 47–59.
13 Sharp, K., Fine, R. and Honig, B., Science 236 (1987) 1460–1463.
14 Northrup, S.H., Boles, J.O. and Reynolds, J.C.L., J. Phys. Chem., 91 (1987) 5991–5998.
15 Wendoloski, J.J., Matthew, J.B., Weber, P.C. and Salemme, F.R., Science 238 (1987) 794–796.
16 Liang, N., Pielak, G.J., Mauk, A.G., Smith, M. and Hoffman, B.M., Proc. Natl. Acad. Sci. U.S.A., 84 (1987) 1249–1252.
17 Currey, K.M., Peterlin, B.M. and Maizel Jr., J.V., Virology, 148 (1986) 33–46.
18 Liebman, M.N., Enzyme, 36 (1986) 115–140.