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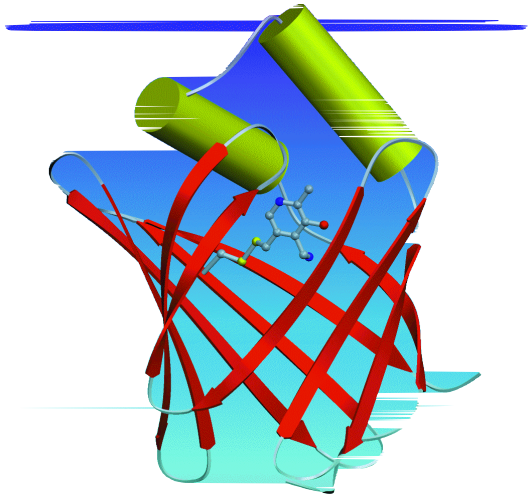
Researchers Are Devising New Protein Catalysts

in this issue

What if you needed a protein that would catalyze a chemical reaction of your own choosing-perhaps a reaction not normally found in nature or a reaction that takes place, but very slowly? Could you use the available database of molecular structures to choose and alter an existing protein to do the job? University researchers are seeking answers to these questions and taking the first steps toward devising new protein catalysts by altering certain proteins so that they function as enzymes. Enzymes are a special form of biological macromolecule that catalyze biochemical reactions with very high selective properties and turnover rates. Highly selective reactions discriminate between structurally close, but not identical, reactants. Turnover rate is defined as the number of reactant molecules that are changed per minute per enzyme molecule.

The researchers are investigating the possibility of using proteins as frameworks for the design and testing of molecular apparatuses that can catalyze new chemical reactions-an area of research that combines the principles of chemistry, structural biology, and the computational sciences. Two groups at the University of Minnesota are collaboratively constructing new catalysts using the framework of a protein molecule that is normally involved in fat metabolism and has no enzymatic activity of its own. The molecular structure of this protein (Adipocyte Lipid Binding Protein, or ALBP) is shown in the accompanying figure. Professor Mark Distefano in the Department of Chemistry and his colleagues Hao Kuang, Ron Davies, and Aram Mazhary have chemically altered ALBP by attaching extra atoms which would catalyze a reaction involving the production of a keto acid from an amino acid. This work was first put to the test by observing whether the products of the reaction were mainly of one conformation, or stereoisomer. Stereoselectivity was seen, offering evidence that a chemical reaction had occurred and that ALBP may, indeed, be functioning as an enzyme. Establishing this stereoselectivity is the first step in devising new protein catalysts.



Chemically altered molecular structure of Adipocyte Lipid Binding Protein

Next, Jeramia Ory, a graduate student in the laboratory of Professor Len Banaszak in the Medical School's Department of Biochemistry, determined the crystal structures of the modified proteins. One of the "new" proteins can be seen in the accompanying figure.

Determining the crystal structures in subsequent studies required the use of the computational resources at the Supercomputing Institute. When knowledge of the positions of most of the atoms in the modified protein is obtained from the crystallographic coordinates, an attempt can be made to analyze the source of the stereoselectivity and to redesign the protein to improve its catalytic properties or turnover rate. The figure on page one shows a ribbon diagram of the structure of the modified ALBP molecule with the extra atoms, a pyridoxamine group, shown as ball and sticks. Notice how the pyridoxamine is totally surrounded by the protein. The results show that the protein framework only allows molecules access to the pyridoxamine from one side.

Modeling Electrochemical Electron Transfer Rates

Cuprous-cupric electron transfer is believed to play a role in limiting rates of stress corrosion cracking in some engineering environments-particularly water cooled nuclear reactors, which have incorporated brass components that provide a source of copper. In these environments, cracks in the steel of the reactor are believed to grow by anodic dissolution of metal from the crack interior, which leaves electrons behind. The dissolution process will stop unless there is electron transfer from the region of the crack to ions in the surrounding water. Indirect evidence suggests that this electron transfer step is rate limiting for crack growth.

A program to model and better understand the electron transfer process was undertaken by quantum chemist Larry Curtiss and electrochemist Zoltan Nagy, at Argonne National Laboratory, and J.W. Halley of the Supercomputing Institute and the physics department of at the University of Minnesota. The group is working to elucidate the mechanisms of electron transfer as part of an effort to control the cracking problem.

When the project began, the goal was to model an electron transfer process between solution and an electrode surface at the microscopic, chemically specific level. The ferrous-ferric electron transfer reaction, not specifically implicated in crack growth, was selected for the first analysis because of its relative simplicity. The group constructed models using molecular dynamics techniques coupled to quantum chemical calculations of potentials for the forces on the reactant and product ions. These permitted calculation of barrier heights, transfer coefficients, and equilibrium potentials. These compared well with the results of experiments that were carried out for the first time at up to 300º C, the temperature at which

reactors operate.

Though work continues on the ferrous-ferric reaction rate, it is clear that the barrier to this reaction arises from the fact that the six neighboring water molecules around the ferric ion are closer to the ion than they are when the ion has accepted an additional electron and becomes a ferrous ion. The energy cost of moving the water away from the ferric ion until the ion can accept an electron is the main origin of the barrier to electron transfer from the electrode. This is called solvent rearrangement. Another important conclusion of the ferrous-ferric study was that the reaction is nonadiabatic (i.e., diabatic), meaning that the two ionic states experience only weak quantum mechanical mixing near the electrode, so that the problem can be treated in perturbation theory.

Most recently, the group has undertaken study of the more corrosion-relevant cupric-cuprous electron transfer. Measurements indicated a barrier height of 32 ± 5 kJ/mol for the reaction. Calculations were made assuming that the reaction is nonadiabatic, like the ferrous-ferric one, and yielded a predicted barrier of 100 ± 20 kJ/mol. Because the molecular dynamics model predicted solvation energies within a few 10s of kJ/mol of the experimental ones, the discrepancy with the barrier heights was not thought to be attributable to calculational error. In seeking a cause for the discrepancy, Sean Walbran of the Halley group suggested that the reaction might be adiabatic.

The accompanying figure contrasts calculated cuprous-cupric free energy surfaces in the adiabatic and nonadiabatic cases. The plunge near the electrode surface is a manifestation of the plating out of copper on the surface which does, in fact, occur. The predicted barrier height, assuming adiabaticity, is 50 ± 40 kJ/mol, which is in better agreement with experiment. In this adiabatic scenario, the cuprous-cupric transfer mechanism is also different than in the ferrous-ferric case. In the adiabatic case, the barrier is due to the need for the copper ion to approach the electrode, whereas in the ferric-ferrous case it was due to the energy required for solvent rearrangement. These two reaction path directions correspond to the z and DE directions in the figure, respectively. Equilibrium occurs for the ferric-ferrous case when there is a large charge on the electrode. In this case, the easiest way for the transfer to occur is solvent rearrangement with the ion far from the electrode where mixing is weak. In the copper case, a small charge on the electrode allows closer approach and strong coupling. In the future the large uncertainty in the calculated barrier height, which arises from uncertainties in the matrix element coupling reactant and product, will be reduced by using direct dynamics techniques that recalculate electronic structure at each stage of a molecular dynamics calculation. The enhancement of the electron transfer rate by chloride adsorbed on the surface is also being studied by the same methods.

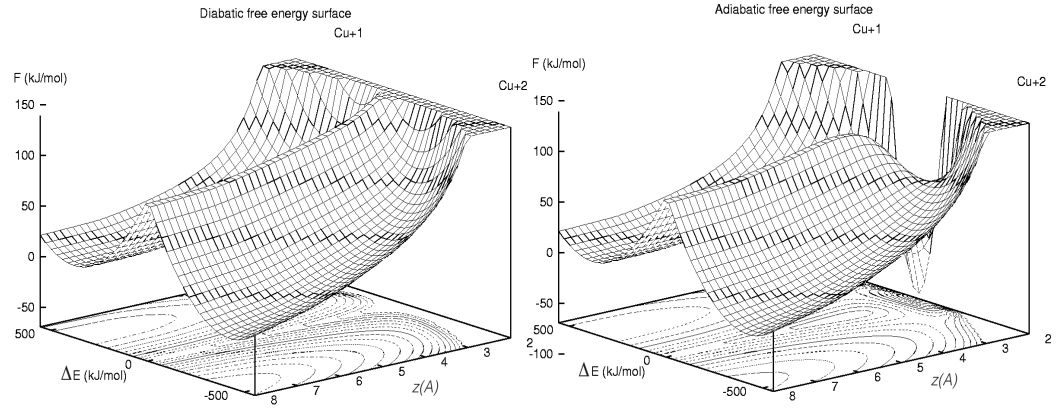


Figure 1: Free energy surfaces for the cuprous-cupric electron transfer reaction calculated from molecular dynamics simulation. The surface at the left is calculated assuming that the reaction is nonadiabatic, while at the right it is assumed to be adiabatic. The z axis is the distance of the ion from the electrode surface, and DE is a measure of the amount of solvent rearrangement.

Precipitation Predictability for Climate Studies

The inherently chaotic behavior of the atmosphere makes it very difficult to accurately predict atmospheric variables at all space-time scales. Despite a decade of considerable progress in atmospheric modeling, prediction of the onset, duration, location, and spatial variability of precipitation remains a challenge. Adding to the problem is the fact that regional climate models and global circulation models are run over large domains and provide information only on large grid scales. This makes it difficult to interpret the impact of climate change or climate variability on water resources management, which requires information at much smaller scales.

University of Minnesota Professor Efi Foufoula-Georgiou and her co-workers, Ph.D. students Alin Carsteanu and V. Venugopal, former Ph.D. student Sanja Perica (now of the Office of Hydrology at the National Weather Service in Maryland), and Shuxia Zhang of Ohio State University, are working to adapt large grid scale atmospheric models for application to smaller-scale hydrologic problems. The group has developed a spatial rainfall downscaling scheme that can be used to disaggregate the results of regional or global models down to watershed scales for hydrologic applications.

Their innovative dynamical/statistical hybrid approach is based on having unraveled a link between larger-scale dynamics of the atmosphere and smaller-scale statistics of rainfall fields. Specifically, the group found that normalized rainfall gradients (obtained via wavelet transform of rainfall intensities) exhibit self-similarity over a significant range of scales. This means that variability at one scale relates to variability at another via a simple transformation that is a function

of the ratio of the two scales. They also discovered that the scale-invariant parameter of this transformation is strongly related to the convective instability of the pre-storm environment (measured by the convective available potential energy, or CAPE). These findings were confirmed by analysis of a large number of radar-monitored warm-season storms, called mesoscale convective complexes, in the Midwest. Based on these findings, a precipitation downscaling scheme was developed using an inverse wavelet transform procedure. Figure 1 shows the results of applying the developed scheme to downscale rainfall from 64 x 64 km^2 to 4 x 4 km^2 grid averages. The figure shows that the disaggregated (simulated) field compares well to the actual field. The only input to the model was the large-scale (64 x 64 km^2) rainfall averages and the value of CAPE at the pre-storm environment.

Accurate representation of the small-scale precipitation variability obviously will improve the prediction of other hydrologic variables, such as surface runoff peak and volume, which are used for water resources design, management, and operation. The question arises, however, as to whether there is a double advantage in trying to capture the small-scale precipitation variability in large-scale atmospheric models. Indeed, the group's results indicate that the inclusion of subgrid-scale rainfall variability and consideration of the small-scale land-atmosphere feedback effects can significantly affect surface temperature predictions-and even the short-term prediction of rainfall intensity itself (see figure 2). This is because redistribution of the large-scale rainfall average within the grid box (i.e., using the bottom right field of figure 1 instead of the top field) causes redistribution of soil moisture and alters the small and large scale land-atmosphere system dynamics. These findings point to the importance of understanding subgrid scale convection processes and cloud microphysics, as well as the significance of including subgrid scale precipitation parameterizations interactively, even in large-scale climate prediction models.

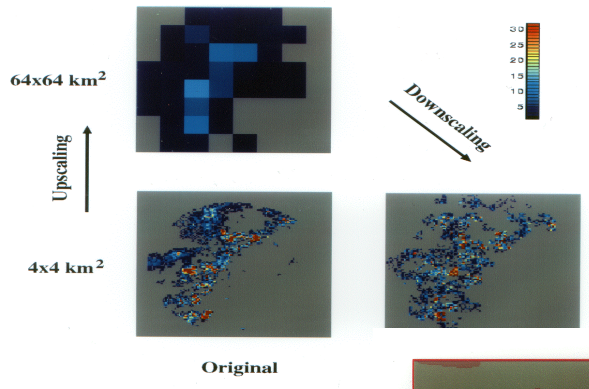


Figure 1: A June 27, 1985 storm over Kansas and Oklahoma at 0300 UTC. The bottom figure in the left column shows the original radar data at 4 x 4 km^2 resolution. From these data, rainfall fields at lower and lower resolutions were obtained by averaging up to 64 x 64 km^2 fields, as shown in the top panel (upscaling). Then, using the 64 x 64 km^2 field and the downscaling scheme of Perica and Foufoula-Georgiou, rainfall fields at higher resolutions were reconstructed down to the resolution of 4 x 4 km^2, as shown in the bottom right panel. A good agreement was found between the rain patterns and the areas

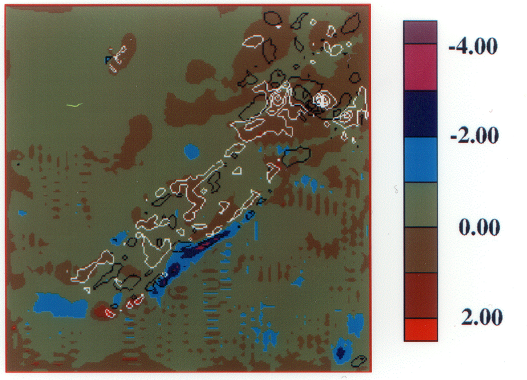


Figure 2: Changes in ground temperature in ºC (color variation) and rainfall intensity in mm/h (black and white curves) caused by adding the feedback effect of subgrid-scale rainfall variability to the simulation of an extreme Midwestern storm on June 11, 1985 over Oklahoma. The Penn State/National Center for Atmospheric Research mesoscale modeling system with two nested domains of 36 km and 12 km, respectively, was

used for this simulation. The comparison (differences in values between the run without and with subgrid scale parameterizations) is shown for a domain of 12 km resolution. The black and white curves indicate the increase and decrease of rainfall intensity with peak values of 55.2 mm/h and 66.6 mm/h, respectively.

Seminar Synopsis

Future Challenges for Scientific Simulation

John R. Rice
Computer Sciences Department
Purdue University
West Lafayette, Indiana

Past and future trends for raw computing power and for software productivity were the topics of Rice's seminar. These trends will greatly enlarge the scope of feasible scientific simulations, said Rice. He discussed the scientific challenges to achieving these simulations and presented potential approaches.

Available computing power (determined by hardware and algorithms) directly determines the feasibility of potential approaches to simulation. In recent decades, hardware power has grown at an astounding rate. Equally astounding advances in algorithm power have been achieved. The combined effect of these advances is to increase our power by 12 to 20 orders of magnitude for many real simulations.

Programming is another key component in simulation. Increases in the productivity of writing computer codes in FORTRAN, C, Java, etc. are very low. The result is that programming is now the principal cost in simulation, and therefore new approaches, such as problem-solving environments, are needed. Five future challenges for scientific simulation were discussed in some detail. These challenges are: multi-physics phenomena, multi-scale phenomena, control, validation of simulations, and improved algorithms. The first three are application areas that are moving into the feasible range because of increasing computational power. Validation is increasingly important as the complexity of the simulations increases. Not only does uncertainty increase with complexity, but the penalty for failure also increases. The final challenge, said Rice, is that increased hardware power is not enough-we must (and can) also increase algorithm power.