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Providing a New Look at Large Biomolecules

A new method for studying the electrical landscape of large biological molecules may enable researchers to make a leap from modeling molecules of 50,000 atoms to those of more than a million atoms.

The technique, developed by Howard Hughes Medical Institute (HHMI) researchers at the University of California, San Diego (UCSD), was used to model the electrostatic properties of microtubules, which are part of the cell's structural and transport systems, and ribosomes, which are the cell's protein-making factories. The scientists say their new computer modeling method, called parallel focusing, will provide molecular biologists with a useful tool for exploring the dynamic behavior of complex biomolecules. The scientists plan to make their software widely available to the scientific community.

"Electrostatic models portray how the charges on individual atoms of a molecule interact to produce a distribution of electric fields throughout the molecule. Shown here are two images that illustrate the electrostatic properties of the microtubule. Potential isocontours are shown along the solid blue surface and the translucent red surface of the microtubule. The "negative" and "positive" ends of the microtubule are shown in the left and right figures, respectively."

Electrostatic models portray how the charges on individual atoms of a molecule interact to produce a distribution of electric fields throughout the molecule. These models have proven useful to researchers analyzing the stability and dynamic motions and interactions of biological molecules, including proteins, DNA and RNA.

In an article published online on August 21, 2001, in *Proceedings of the National Academy of Sciences*, researchers led by HHMI investigator J. Andrew McCammon report that parallel focusing is a new approach to solving the Poisson-Boltzmann equation (PBE), a fundamental equation in the field of electrostatics.

"One of the problems with traditional molecular dynamics methods for simulating large systems is that they require considerable computational effort to simulate the surrounding atoms of the aqueous solvent," said McCammon. "The Poisson-Boltzmann equation circumvents this by treating the solvent as one featureless polarizable medium — essentially a big cloud of charge around a molecule such as a protein," he said.

According to McCammon, the effectiveness of the PBE, which is called an "implicit solvent method," has made it one of the most popular bases for electrostatic modeling. But while the popularity of the PBE has increased, methods to solve the equation have been limited to molecules of about 50,000 atoms because of their considerable computational demands.

In the *PNAS* article, however, McCammon, HHMI predoctoral fellow Nathan A. Baker and their colleagues at UCSD describe how the parallel focusing method enables solution of the PBE to be run efficiently and flexibly on parallel computers. By using massively parallel computers, researchers can divide large computations among many processors, and drastically reduce the time required to create complex models.

Electrostatic modeling typically represents the biomolecule and the PBE on a Cartesian grid, explained Baker. Very fast numerical methods, such as the multigrid, are then used to solve the equation on this grid. The solution on the array of grid points is then used to represent the electrostatic potential around the biomolecule.

"One can think of these electrostatic equations as being solved in a very big box that contains the grid and which is several times larger than the molecule to be modeled," said Baker. "In the parallel focusing method, we divide that box up, so that even if it's a very large box, the calculations can be done on a single processor. We have each processor solve the equations for that coarse grid and then use that low-accuracy solution to provide the boundary conditions to focus on a much smaller and finer problem on a particular partition of the mesh allocated to that particular processor."

Parallel focusing is based on theoretical work by UCSD mathematicians Randolph E. Bank and Michael J. Holst, who proved that solving a problem with a low level of accuracy over an entire domain would enable one to use that solution to get a more accurate picture on a subset of that domain, Baker said. According to Baker and McCammon, their approach enables each processor to arrive at a highly precise solution for a tiny part of a molecule, without the need to communicate with other processors in the parallel computer. Reducing or eliminating such communications is critical if parallel machines are to tackle the problems efficiently.

Parallel focusing allows electrostatic modeling of molecules with a very high resolution, in which each partition of the mesh represents about 0.5 Angstroms. McCammon and Baker say that the method can be used on a range of parallel computers — from networks of workstations with relatively low-speed connections to high-performance supercomputers.

To demonstrate the utility of their approach, the scientists modeled the electrostatic charges on microtubules and ribosomes. Microtubules are hollow polymers of protein that provide a rigid support structure in the cell and serve an important role in transporting proteins throughout the cell. Ribosomes are large molecular complexes of RNA and protein that are the site of protein synthesis in the cell.

Applying their technique to a model of a 1.25-million-atom microtubule, which was composed of 90 units of the protein tubulin, revealed that electrostatic variations in the microtubule were much larger in scale than those seen in individual tubulin molecules. The large-scale "undulations" in electrical potential demonstrate the value of this type of modeling technique in revealing the collective properties of large molecules, said Baker. The scientists also found that the electrostatic potential at each end of the microtubule was different. This may provide clues to the stability of microtubules, Baker said.

The scientists also explored the variation in electrostatic potential over the sites on the microtubules where drugs like Taxol bind. "Understanding microtubule instability and the mechanism by which microtubules dissociate could have therapeutic applications because many anti-cancer drugs act to stabilize microtubules," said McCammon.

The electrostatic model of the two ribosomal subunits — one with 88,000 atoms and the other with 94,854, revealed an intricate map of positive and negative potential that could yield insights into the function of ribosomes, said the scientists.

According to McCammon, software using the new approach will soon be made available to researchers to help guide their experiments on large molecules. The scientists will also begin extending their method to model dynamic changes in molecules over time. "This approach enables investigators to do all the things they could do with electrostatic models before — for example, exploring binding energies and associations of proteins — on a far larger scale that is much more relevant to cellular processes," said McCammon.