SimbiosNews

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Accurate Molecular Dynamics Force Fields for the Scientific Masses

Many have long hoped that molecular dynamics calculations—the computation of how molecules move and interact with other molecules—would revolutionize the world of synthetic chemistry, especially for the design of new drugs. That hasn't happened yet, but with the recent integration of the more accurate AMOEBA polarizable force field with the OpenMM software, we are one step closer.

"It's a really important time," says **Vijay Pande, PhD**, associate professor of chemistry and of structural biology at Stanford University and the lead of the OpenMM project. Now that there are better, faster molecular dynamics tools, such as OpenMM, the next question for the community is "can we then get better precision to understand the failures of models and develop better, more accurate models?" Early results from OpenMM-AMOEBA suggest we can.

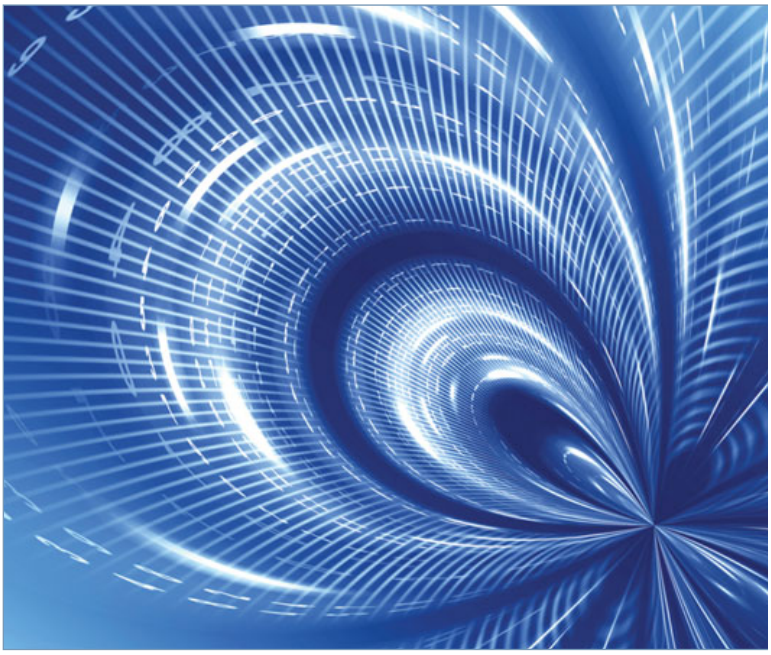
Classical models of chemistry rely on mechanical concepts to describe the behavior of molecules. Bonds between atoms are treated as springs; the electrostatic forces that repel or attract particles to one another are computed using just the electrical charges of and distance between two particles (Coulomb's law); and the partial electrical charges assigned to an atom remain constant, regardless of its environment.

In contrast, the AMOEBA model, which is implemented in the TINKER molecular dynamics package, includes many more parameters and interactions for computing the electrostatics. "With AMOEBA, you have charges; you have dipoles; you have induced dipoles; you have quadrapoles…," explains **Mark Friedrichs, PhD**, the lead software engineer of the OpenMM-AMOEBA integration. In addition, AMOEBA includes polarization effects—the response of a particle's charge to its changing environment.

Jay Ponder, PhD, associate professor of chemistry at Washington University in Saint Louis, and the developer of the AMOEBA force field, says that "it's crazy" to omit these effects, as has been done for so long. "The charge and the electrostatic potential field around say a carbonyl oxygen should be different when it's exposed to solvent or if it's hydrogen-bonded in an alpha helix in a protein."

AMOEBA's additional complexity does improve the accuracy of the calculations. "Typical force fields have an error of about 1 kilocalorie per mole per amino acid when computing the free energy to go from the water to gas phase," explains Pande. That error can grow to be quite large, especially when dealing with systems of hundreds or thousands of amino acids. "AMOEBA has already demonstrated that it can decrease that error by a factor of 4. That accuracy is very exciting."

The problem is that the complex AMOEBA model is much slower at generating results than the classical models. "Instead of computing Coulomb's law, which is one line of computer code, we have massive piles of algebra that we have to do," says Ponder.



"That significant slowdown has sometimes been really hard for people to swallow," says Pande. So he and his team have integrated AMOEBA with their OpenMM library that is designed for speeding up molecular force fields on high-performance computer architectures, such as graphics processing cards (GPUs).

The integration resulted in speedups "on the order of 50 for calculations in explicit solvent and factors of 100 or more for implicit solvent, depending on the system size," says Friedrichs. And there are plans to further optimize the code.

"This new generation of force field models—polarizable models—has to be made available in such a form that people can prove to themselves that they're getting substantially better results, if they're going to catch on," says Ponder. "So having AMOEBA implemented in something like OpenMM is a tremendous thing." □

DETAILS

Support for the AMOEBA force field is provided in OpenMM release 3.0 and later. You can download OpenMM from http://simtk.org/home/openmm. The project wiki also provides more benchmark numbers. Learn more about AMOEBA and TINKER at http://dasher.wustl.edu/tinker.

Simbios (http://simbios.stanford.edu) is the National Center for Physics-Based Simulation of Biological Structures at Stanford.