Accurate and computationally efficient solvent models for biomolecular simulations. Progress in modern bio-molecular sciences, from structural biology to structure-based drug design, is greatly accelerated by methods of atomic-level modeling and classical simulations that bridge the gap between theory and experiment; 12,000+ research papers that use these methods are published each year. Accurate and computationally facile water models are just as important for outcomes of these studies as water is for Life. However, critical accuracy gaps remain: For example, even with most detailed (explicit, Fig. 1 left) water models, unacceptably large discrepancies with experimental binding free energies, and sensitivity to the model, are seen for ligand binding systems, which hampers rational drug design efforts. Implicit water models (Fig. 1 right), in which discrete water molecules are replaced by a continuum with key properties of liquid water, is a promising alternative, but making the idea work in practice proved difficult.

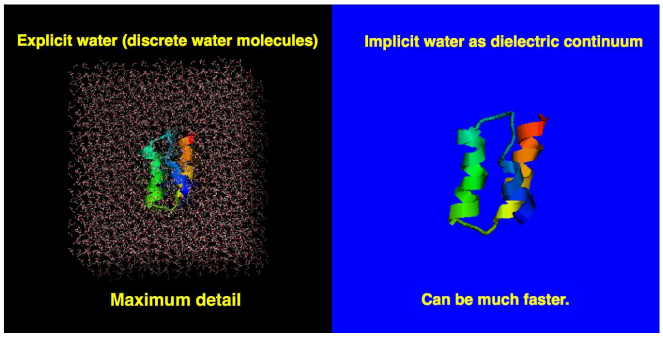

Figure 1: Two principle approaches to representing aqueous solvation in classical biomolecular simulations. **Left:** Explicit solvation, in which the biomolecule of interest is embedded in a large "box" of discrete H_2O molecules, and **Right:** Implicit solvation, which treats solvent as a continuum with the dielectric and non-polar properties of water.

One of my early contributions in this area was the development of a version of the implicit water model that worked well for practical atomistic simulations of macromolecules; the challenge was to keep the model computationally facile while adding the right physics elements to it. The model developed, GB-OBC,[1] is now implemented in every major atomistic modeling package, and is being widely used in problems ranging from protein folding to docking. Further progress required several critical insights into physical and computational aspects of aqueous solvation,[2] and into biomolecular electrostatics in general; these insights have laid the foundation for subsequent critical improvements, by others and by my group, to the implicit solvent models. One of the group's more recent achievement in this area is an implicit water model (GBNSR6[3,4]) that, so far, has proven to be more accurate than other models of the same class (generalized Born) available in major simulation packages.

Recently, we expanded our efforts into the area of classical explicit solvent models (Fig. 1 left), the type still most widely used today. Currently available water models of this class are local optima in the parameter space, they still fail to reproduce several key water properties accurately and simultaneously, which is the fundamental unresolved problem in this field. Critically, even modest inaccuracies of water models can drastically and adversely affect outcomes of atomistic biomolecular modeling. Specifically, we have proposed a completely novel way of constructing highly accurate models of this type. The resulting water model[5,6] is a hard-to-find *global* optimum in the relevant parameter space. The model "OPC" has already shown significant promise in several types of practical biomolecular simulations. We are now using the global optimization approach to develop even more accurate water models – so called "polarizable" models.

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