for the Born radii stochastically, the exact Born radii can be computed without the need for multiple expensive deterministic calculations. In addition, although the proposed method strictly works only on a van der Waals surface, it can be modified to closely match the predictions of the linearized Poisson-Boltzmann equation on a solvent-excluded (SE) surface by determining prior to the calculation which spheres are not solvent exposed in the SE surface and inflating these spheres by the probe radius. Additionally, because the predictions of this method can be made arbitrarily close to those given by exact Born radii, this method can be used to evaluate the ability of the Born approximation to reproduce the electrostatic binding free energy given by the Poisson-Boltzmann equation independently of the approximations usually made to derive the Born radii. This study presents the results of such an investigation for a broad range of biomolecular complexes.

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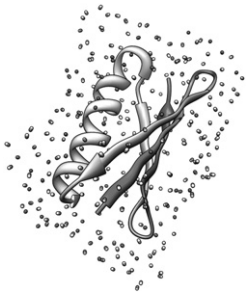
Accurate Solutions with the Semi-Explicit Assembly Water Model
Christopher J. Fennell[1], Charles W. Kehoe[2], Ken A. Dill[1].
[1]Stony Brook University, Stony Brook, NY, USA, [2]UCSF, San Francisco, CA, USA.
Molecular simulations that are computationally cumbersome using explicit solvent models can be more tractable with implicit solvents. However, such continuum solvent approaches can struggle when the discrete nature of water is needed, often at the solute/solvent interface. We have developed a new solvation method, called Semi-Explicit Assembly (SEA), that merges the best of both routes - the efficiency of an implicit solvent with the microscopic detail and accuracy of an explicit solvent. Here, we give an overview of SEA and highlight some of our recent developments and applications. These include new continuum boundary treatments, application to larger biomolecules, and performance in studies involving blind predictions of solvation free energies.



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Improving Implicit Solvent Models with Differential Geometry
Dennis G. Thomas, Jaehun Chun, Nathan A. Baker.
Pacific Northwest National Laboratory, Richland, WA, USA.
Implicit solvent models are popular for their high computational efficiency and simplicity over explicit solvent models. Hence, there has been significant interest in testing and improving these models for their ability to accurately compute the thermodynamic properties of a wide range of chemicals and macromolecules. One such model is a differential geometry-based solvation model where a generalized geometric flow (GF) equation and a generalized Poisson-Boltzmann (PB) equation are self-consistently solved to compute a smooth dielectric profile, and the polar and non-polar solvation free energies. The GF equation contains the polar energetic terms defined by the PB equation, and non-polar energetic terms describing the pressure-volume work to create a cavity in the solvent, energy to create a solute-solvent interface, and solute-solvent attractive dispersion interactions. The solution to the GF equation is a characteristic function that describes a smooth solute-solvent boundary. This function defines the smooth dielectric profile used in the PB equation to compute the electrostatic potential. Therefore, the main parameters of the model are the solute/solvent dielectric, solvent pressure, surface tension, solvent density, and molecular force-field parameters. As for other solvation models, these parameters have to be determined by experimental conditions or optimized against experimental solvation energy data before the model can be applied for new molecules. However, it is not clearly understood how different choices of the model parameters are coupled with force field choice to affect the computed results. In this work, we have performed a parametric study on the GF-based solvation model to investigate how changes in the pressure, surface tension and use of different force fields affect the optimal solutions to the solvation free energies of small organic molecules. Results of this model will be presented for a set of 17 small organic molecules using three different force fields.

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Coarse Grained Ion-Ion and Ion-Water Interactions
See-Wing Chiu, Eric Jakobsson.
Univ. of Illinois, Urbana, IL, USA.
A detailed knowledge of ion transfer mechanisms between water and low-polarity media is crucial for many areas of chemistry and biochemistry such as phase transfer catalysis, separations, and biomembranes. [1,2] It has become clear from experiments [3] and simulations[4] that the transfer of small hydrophilic ions from water to an immiscible organic liquid is typically accompanied by the co-transfer of several water molecules. As a result, the ion exists in the organic phase as a hydrated cluster. To properly simulate biological phenomena at the coarse grained (CG) level, a proper treatment of the hydrated ions and solvent is crucial and is nontrivial. We have recently parameterized an uncharged and 4:1 mapped CG water with 3 interaction sites based on a generalized Morse -like potential which has greater flexibility in tuning the landscapes of CG effective pairwise potentials. [5] This new CG water becomes polarizable when it interacts with ions (Na+, Cl-) and or any other charged sites but not among its own species. The Morse interaction parameters for the CG ion-ion, ion-water, and ion-alkane are to be parameterized against the free energy of transfer of ions between water and liquid alkanes as well as radial distributions of ion-ion and ion-water. The target data are to be derived from atomic simulations.
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Predicting Bound Ions on the Protein Surface
Marharyta Petukh.
Clemson University, Clemson, SC, USA.
Biological macromolecules exist in the complex environment of the cell, constantly interacting with other molecules and ions. Some of the ions may bind directly to proteins affecting their structure and thus altering their function. Though the X-ray crystallography remains to be one of the most popular methods of proteins structure determination, typically the positions of bound ions are not routinely revealed. Here we report a development of an approach, based on numerical solutions of the Poisson-Boltzmann equation (PBE) as implemented in DelPhi, which predicts the positions of surface bound ions taking into account geometrical considerations as well. The method is tested against existing experimental data of proteins with different types of ions on the surface and it is shown that it the electrostatic potential is the dominant factor for ion binding not involving chemical interactions. We further outline the importance of such an approach with respect to relaxing the limits of Poisson-Boltzmann formalism in describing the perturbation of ion's concentration in the space regions with large local electrostatic potential. The work is supported by NIH, NIGMS, grant number 1R01GM093937-01.

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Towards Fast and Accurate Calculation of Protein pKa Values Exploiting Various Degrees of Conformational Flexibility
Krishna Praneeth Kilambi, Jeffrey J. Gray.
Johns Hopkins University, Baltimore, MD, USA.
Virtually every biological process is pH dependent. Many fundamental biological phenomena including protein folding, enzyme catalysis, protein-protein interactions and pathological conditions are profoundly influenced by the pH of their environment. Accurate prediction of the pKa values of residues that can adopt variable protonation states would be a significant step towards probing the effects of pH on proteins. Despite the progress in pKa prediction algorithms, developing a method that can incorporate extensive protein conformational flexibility while retaining a relatively small computational resource footprint remains a significant challenge. We developed a fast and accurate method to predict pKas of residues that commonly exhibit variable protonation states in proteins. The algorithm