160d Development of Polarizable Force Fields for Application to Molecular Dynamics Simulations of Biological Molecules

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Classical statistical mechanical methods such as molecular dynamics (MD) and Monte Carlo (MC) approaches are routinely applied to study a broad spectrum of biological systems comprised of proteins and nucleic acid based molecules. At the heart of such methods is the force field governing the nature of interactions between constituent entities and allowing for the determination of dynamics from forces deriving from them. One component of the force field is the electrostatic interaction, often modeled via a Coulomb pair potential between two sites assigned representative charges. The charge distribution, often determined from ab initio calculations on representative systems in vacuum, represents some average, mean-field representation of the environment of the molecule. Of course, such a mean-field approximation is not rigorous for treating systems with strong anisotropy, examples being the interfacial region between a solvated protein and its solvent (usually water), the differing dielectric environments encountered by an ion trans-locating through a narrow ion channel from the extra-cellular milieu to the cytoplasm, and finally, the interfacial region between two homogeneous fluids (or the pure liquid-vapor interface).

We will discuss our efforts in developing force fields, for application to protein systems, which allow for electronic response to local environment, and in this sense are termed polarizable force fields. The model is based on the idea of charge equilibration (or electronegativity equalization) that allows for redistribution of charge between atoms in a molecule based on the local chemical environment(1). The approach is fundamentally based on the density functional theory of atoms in molecules(2). The movement of charge is governed by empirical parameters of the electrostatic model that are determined based on charge perturbations calculated using density functional methods (DFT). The force field is then completed by assigning the dispersion parameters (typically the Lennard-Jones 12-6 functional form) based on simulations of pure liquids as well as gas-phase dimers of representative solutes and water; the approach is taken to maintain a balance between solute-solute, solute-solvent, and solvent-solvent interactions.

We will further discuss application of the force field to small model compounds, focusing on pure liquid properties such as enthalpies of vaporization, densities, diffusion constants, and distributions of molecular dipole moments naturally arising due to the inclusion of polarizability. We finally validate the force field for protein systems by applying the force field to study the properties of six small proteins spanning the known secondary structural motifs via molecular dynamics simulations in explicit polarizable water.

Finally, we will address concurrent work involving parameterization and application of polarizable force fields to ion channel systems where there has been strong indication in the recent past suggesting the need for some explicit representation of polarization to achieve quantitative predictions of ionic currents in model ion channel systems such as the gramicidin A channel.

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