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DelEnsembleElec: Computing Ensemble-Averaged Electrostatics Using DelPhi

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Abstract. A new VMD plugin that interfaces with DelPhi to provide ensemble-averaged electrostatic calculations using the Poisson-Boltzmann equation is presented. The general theory and context of this approach are discussed, and examples of the plugin interface and calculations are presented. This new tool is applied to systems of current biological interest, obtaining the ensemble-averaged electrostatic properties of the two major influenza virus glycoproteins, hemagglutinin and neuraminidase, from explicitly solvated all-atom molecular dynamics trajectories. The differences between the ensemble-averaged electrostatics and those obtained from a single structure are examined in detail for these examples, revealing how the plugin can be a powerful tool in facilitating the modeling of electrostatic interactions in biological systems.

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Key words: DelEnsembleElec, ensemble-averaged electrostatics, Poisson Boltzmann equation, DelPhi, molecular dynamics, influenza glycoproteins.

1 Introduction

Electrostatic interactions play an essential role in the dynamics of biological systems. These forces are the predominant long-range interactions influencing the dynamics within and between biomolecules, thus the accurate treatment of electrostatics is necessary for detailed models of these systems. The electrostatic interactions associated with ionic and polar chemical groups found in proteins, nucleic acids, lipids, and other biomolecular systems are essential to both their structure and function [1].

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A variety of methods exist for computing the electrostatic interactions within the context of classical Molecular Mechanics (MM) models. The electrostatic energy and potential may be obtained by computing the pairwise Coulomb interaction between all atoms, and many approximate methods exist to efficiently estimate these interactions. While the computation of pairwise interactions is computationally expensive, scaling as the square of the number of atoms in a system, methods such as the Particle-Mesh Ewald (PME) [2] algorithm for periodic systems and the Fast Multipole Method (FMM) [3] can significantly reduce the complexity of computation by introducing well-controlled approximations.

The Poisson-Boltzmann (PB) equation is an attractive method for computing the mean-field potential of biomolecules [4]. By modeling the solvent environment as a continuum dielectric and salt ion distribution, the electrostatic potential and electrostatic free energy of a biomolecule may be estimated under the given conditions. In most implementations, the solvent provides dielectric screening of the biomolecule potential, represented as a uniform dielectric constant, while the salt is modeled based on the potential values within the continuum solvent by a nonlinear term in the PB equation. A linearized PB treatment of salt effects is accurate for proteins with modest net charges in monovalent salt solutions, while the more sophisticated treatment of salt with the nonlinear form of the PB equation is often used in treating multivalent salt solutions and in modeling highly charged polyelectrolytes such as nucleic acids [5]. Many methods of solving the Poisson-Boltzmann equation such as presented here in DelPhi utilize the finite difference method to efficiently solve the electrostatic potential on a discretized grid [6].

Realistic treatment of biomolecular dynamics requires ensemble sampling to understand the conformational flexibility of these molecules within their chemical environment. All-atom explicit solvent Molecular Dynamics (MD) is a widely accepted method for generating a canonical distribution of states for biomolecules modeled using Molecular Mechanics force fields such as AMBER [7] and CHARMM [8]. By averaging over the trajectory of states produced in these simulations, ensemble properties such as the electrostatic potential may be obtained, giving insight into thermodynamic properties of these systems. This approach has been useful in previous studies of biomolecular systems, such as in understanding the electrostatic environment of protein-bound drugs [9] and in understanding the transport of ions and biomolecules through membrane pore proteins [10]. Notably, the use of ensemble information in particular, as opposed to a single static structure, when computing the electrostatic properties of dynamic biomolecules has been shown to increase agreement of the computed values with experiment [9].

To facilitate the calculation of ensemble-averaged electrostatic properties with the Poisson-Boltzmann equation, we have developed a plugin interface for the visualization software package VMD [11], which interfaces with the DelPhi numerical PB equation-solving software package [6, 12]. This plugin computes the ensemble electrostatic potential and free energy of biomolecules from their trajectories in VMD-compatible formats such as those used in the MD packages AMBER and CHARMM. A graphical user frontend provides a simplified interface for specifying all the individual options supported