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Poisson-Boltzmann Theory of Bionanosystems

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Abstract. The structure and function of BNS (bionanosystems) such as macromolecules, viruses and ribosomes are strongly affected by electrostatic interactions. Yet their supra-million atom size makes them difficult to simulate via a straightforward Poisson-Boltzmann (PB) approach. Here we explore a multiscale approach that results in a coarse-grained PB equation that follows rigorously from the all-atom PB equation. The derivation of the coarse-grained equation follows from an ansatz on the dependence of the electrical potential in two distinct ways, i.e. one reflecting atomic-scale variations and the other capturing nanometer-scale features. With this ansatz and a series expansion of the potential in a length-scale ratio, the coarse-grained PB equation is obtained. This multiscale methodology and an efficient computational methodology provide a way to efficiently simulate BNS electrostatics with atomic-scale resolution for the first time, avoiding the need for excessive supercomputer resources. The coarse-grained PB equation contains a tensorial dielectric constant that mediates the channeling of the electric field along macromolecules in an aqueous medium. The multiscale approach and novel salinity connections to the PB equation presented here should enhance the accuracy and wider applicability of PB modeling.

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Key words: Poisson-Boltzmann equation, multiscale analysis, bionanostructures, viruses, ribosomes, macromolecules.

1 Introduction

Electrostatic interactions play a crucial role in determining the structure and dynamics of proteins and more complex structures (e.g., enzymes, ribosomes and viruses). DNA is overall negatively charged due to phosphate groups, and the inner surface of a viral capsid often has a net positive charge, likely to assist in the import of genetic material

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during viral self-assembly [1]. These bionanosystems (BNS) reside in an aqueous electrolyte, which affects their conformation, stability, and function due to screening and dielectric channeling. Aqueous physiological media contain many mobile ions (e.g., Cl^-, Na^+, K^+, Mg^{++}, and Ca^{++}) which redistribute to screen the Coulomb potential of the fixed charges on the BNS by creating layers of counter-ions. Orientable or polarizable molecules of the host medium also serve to decrease the electrical forces that determine the structure and function of a BNS and its interaction with other features in the system. This accurate calculation of the electrostatic potential could enhance our understanding of BNS [2]. One could, for example, use such calculations to estimate the solvation energy, find pKa values [3], and titration curves for proteins. One could calculate the electrostatic forces between biomolecules for use in molecular dynamics [4]. In carrying out molecular mechanics computations, it is important to account for the channeling of the electric field along a BNS due to the dielectric constant contrast between the aqueous medium and the interior of a protein, an effect not accounted for in $1/r$ Coulomb computations as in the CHARMM force field. Computational challenges are even greater when attempting to model a whole virus or ribosome for therapeutic design or for liposome-cell surface interaction studies associated with the analysis of nanocapsules for the delivery of drugs, genes or siRNA to diseased cells.

The magnitude of the systems of interest can be illustrated by Fig. 1, which shows the capsid of a native cowpea chlorotic mottle virus (CCMV) with atoms colored by charges on them. Fractional charges are assigned according to the CHARMM27 force field. The capsid with 432,240 atoms consists of 180 chemically identical protein subunits that form a 286-Å-diameter icosahedral shell. Each protein subunit is composed of 190 amino acids taking three quasi-equivalent positions on the virus surface. CCMV is one example of the small icosahedral viruses. A typical BNS involves millions of atoms and hence direct PB modeling would require billion grid node computations. Clearly novel methods are needed. The challenge is even more acute when attempting to use PB to compute forces in a molecular dynamics approach. The objective of this study is to investigate methodologies for simulating such supra-million atom systems.

The PB equation has been traditionally used to find the electrostatic potential around a macromolecule. A PB model ignores the volume of ions in the medium. Therefore, PB equation is valid for dilute ionic solutions with several Debye lengths away from the fixed charges on the mesostructure of interest (i.e. *concentration* $\leq 0.15M$) [5]. This model has been applied to calculate properties of molecules in solution [2]. Extensions of the PB model to account for the mobile ions sizes and correlations have been developed [6, 7]. The PB model accounts for solvent molecules implicitly via the dielectric constant ε; ε is low within the molecule, and is assumed to increase gradually to the unperturbed, far field value over several angstroms away from the molecule of interest [8]. Solutions to simple problems with spherical, cylindrical or planar symmetry are available for the linearized PB equation [9, 10]. A closed form formula for the solution of nonlinear PB does not seem to be possible except for the planar case [11] and the infinite cylindrical symmetric case where only counter ions exist in the solution [12].