Hybrid Boundary Element and Finite Difference Method for Solving the Nonlinear Poisson–Boltzmann Equation

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Abstract: A hybrid approach for solving the nonlinear Poisson–Boltzmann equation (PBE) is presented. Under this approach, the electrostatic potential is separated into (1) a linear component satisfying the linear PBE and solved using a fast boundary element method and (2) a correction term accounting for nonlinear effects and optionally, the presence of an ion-exclusion layer. Because the correction potential contains no singularities (in particular, it is smooth at charge sites) it can be accurately and efficiently solved using a finite difference method. The motivation for and formulation of such a decomposition are presented together with the numerical method for calculating the linear and correction potentials. For comparison, we also develop an integral equation representation of the solution to the nonlinear PBE. When implemented upon regular lattice grids, the hybrid scheme is found to outperform the integral equation method when treating nonlinear PBE problems. Results are presented for a spherical cavity containing a central charge, where the objective is to compare computed 1D nonlinear PBE solutions against ones obtained with alternate numerical solution methods. This is followed by examination of the electrostatic properties of nucleic acid structures.

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Introduction

Importance of Nonlinear Electrostatic Modeling

The ability to accurately model the electrostatic properties of highly charged biomolecular systems such as nucleic acids is critical because for such biopolyelectrolytes the structure–function relationships and molecular recognition events are strongly influenced by the electrostatic interactions. Due to the high charge density of its negatively charged sugar–phosphate backbone, the stability and interactions of nucleic acid structures with other charged molecules (e.g., drugs and proteins) are critically dependent on the ion type and concentration in the environment (see refs. 1–3). Because many biological systems contain both monovalent and multivalent ions it is important to model mixed salt solutions.[4] In RNA and many other biomolecular systems both monovalent and divalent ions can trigger conformational transitions and play other important functional roles. For example, the helix-coil transition and folding of nucleic acids are dependent on the nonspecific effects of changes in the concentrations of both monovalent and divalent ions (e.g., refs. 3 and 5–8).

One formulational framework commonly adopted to treat nonspecific electrostatic interactions in highly charged systems is based on the classic continuum electrostatic model. In this model the solvent and dissolved ions are treated as a continuum environment, characterized by the solvent dielectric constant and bulk ionic strength, respectively, but the solute is treated explicitly. The 3D full (nonlinear) Poisson–Boltzmann equation (PBE) is one of the most popular continuum electrostatic approaches. In this method, the solute is treated in atomic detail with partial charges on all atoms and the dielectric interface between the solute and solvent regions is modeled by one of the molecular surfaces (e.g., solvent excluded surface[9]). For highly charged systems the linear PBE is no longer valid and the nonlinear PBE must be employed. For example, it has been shown that for highly charged enzymes such as superoxide dismutase (SOD) the electrostatic potential in the active site region obtained with the nonlinear PBE is weaker relative to the linear PBE case.[10,11] Consequently, the diffusion-controlled reaction rate constants for the SOD–superoxide catalytic reaction obtained with the 3D nonlinear PBE are smaller than those obtained with the linear PBE.[12] The Hecht et al.[13] study shows that much better agreement with experimentally measured electrostatic potential at the surface of calf-thymus DNA is obtained using the nonlinear rather than linear PBE. Moreover, using the nonlinear PBE to predict various electrostatic properties of highly charged systems achieves good agreement with experimen-

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