Formulation of a New and Simple Nonuniform Size-Modified Poisson–Boltzmann Description

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The nonlinear Poisson–Boltzmann equation (PBE) governing biomolecular electrostatics neglects ion size and ion correlation effects, and recent research activity has focused on accounting for these effects to achieve better physical modeling realism. Here, attention is focused on the comparatively simpler challenge of addressing ion size effects within a continuum-based solvent modeling framework. Prior works by Borukhov et al. (*Phys. Rev. Lett.* **1997**, *79*, 435; *Electrochim. Acta* **2000**, *46*, 221) have examined the case of uniform ion size in considerable detail. Generalizations to accommodate different species ion sizes have been performed by Li (*Nonlinearity* **2009**, *22*, 811; *SIAM J. Math. Anal.* **2009**, *40*, 2536) and Zhou et al. (*Phys. Rev. E* **2011**, *84*, 021901) using a variational principle, Chu et al. (*Biophys. J.* **2007**, *93*, 3202) using a lattice gas model, and Tresset (*Phys. Rev. E* **2008**, *78*, 061506) using a generalized Poisson–Fermi distribution. The current work provides an alternative derivation using simple statistical mechanics principles that place the ion size effects and energy distributions on a consistent statistical footing. The resulting expressions differ from the prior nonuniform ion-size developments. However, all treatments reduce to the same form in the cases of uniform ion-size and zero ion size (the PBE). Because of their importance to molecular modeling and salt-dependent behavior, expressions for the salt sensitivities and ionic forces are also derived using the nonuniform ion size description. Emphasis in this article is on formulation and numerically robust evaluation; results are presented for a simple sphere and a previously considered DNA structure for comparison and validation. More extensive application to biomolecular systems is deferred to a subsequent article. © 2012 Wiley Periodicals, Inc.

Introduction

To reliably model the behavior of biomolecules and predict their dependence upon ambient salt conditions and their interactions with other molecules, an accurate and general treatment of the governing electrostatics is essential. Currently, the most widely used characterization of biomolecular electrostatics that accounts for the presence of mobile ions in the solvent, is the Poisson–Boltzmann (PB) description. PB methods adopt an implicit solvent model where the solute is modeled at the atomic level while the solvent is characterized in terms of its macroscopic properties. Among the currently available suite of biomolecular electrostatics modeling methods, PB-based formulations realize a useful compromise between physical modeling fidelity/detail and computational cost. Explicit solvent models offer superior physical realism but require considerably higher computational effort to sample the conformational space by either molecular dynamics or Monte Carlo techniques. Simpler descriptions such as Generalized Borne[1,2] or particle-based Debye–Hückel models,[3] conversely, are less expensive, but do not provide the level of detail of the dielectric interface needed for accurate force predictions and binding sites.

PB-based methods have been successfully applied to characterize counterion distributions and ion competition effects,[4–6] predict titration curves and pK-shifts, obtain the salt-dependent binding affinities and association rates of biomolecular complexes, analyze the electrostatic fields of biological ion channels,[7] simulate molecular recognition events in nucleic acids and other biopolyelectrolytes, and study the effects of salt concentration upon conformational transitions.[8–10] PB-based electrostatics descriptions are also useful in modeling colloidal stability and electrokinetic effects such as electrophoresis and electro-osmosis[11,12] with applications to paper-manufacturing and water purification.

Limitations and cases of failed predictions

Despite such successful applications and widespread use of PB-based electrostatic simulation software, the PB description is subject to important limitations that can become pronounced in some contexts. For example, comparisons against more sophisticated solvent treatments using idealized polyion models[13–15] have shown that while the nonlinear PB equation (PBE) provides good estimates of the ion distributions and electrostatic energies for 1:1 salts at low and moderate salt concentrations, significant discrepancies arise when considering highly charged biopolyelectrolytes immersed in high univalent salt concentration or in multivalent salts. Attraction forces between same-charged molecules in ion channels or close proximity walls[16] are also poorly predicted using the

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