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Electrical double layer: A numerical treatment of stern layer in biomolecular electrostatics

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ABSTRACT

Poisson–Boltzmann equation (PBE) is widely used in the context of deriving the electrostatic energy of macromolecular systems and assemblies in aqueous salt solution. Macromolecules and their ion penetrability with the presence of stern layer have been discussed theoretically and analytically. While numerous numerical solvers for the 3D PBE have been developed, the integral equation formulation for the boundary treatments used in these methods has only been loosely addressed, especially in the ion exclusion stern layer. The default standard in current linear PBE implementations is to estimate the potential at the outer boundaries using the (linear) Debye-Hückel (DH) approximation. However, as assessment of how these outer boundary treatments affect the overall solution accuracy in the stern layer does not appear to have been previously made. As will be demonstrated here, this DH approximation can under certain conditions produce completely erroneous estimates of the potential and energy salt dependencies. In this work, new sets of boundary conditions are invoked that take into account the impenetrability of the ions to the molecule. Using surface integral equation, this new treatment is able to give an accurate description of the electrostatic potential distribution, electrostatic solvation free energy etc. not only in a molecular system by means of continuum model but also focus on physics of the ion impenetrable stern layer. The accuracy of the results obtained by using the boundary element method (BEM) is tested by comparison with analytical Tanford–Kirkwood results for a model spherical solute system. Finally the author also examined how the general ion exclusion layers would tend to increase surface electrostatic potential under physiological salt conditions. To facilitate presentation and computational domain, attention is restricted here to the 3D spherically symmetric linear PBE. Though geometrically limited, the modeling principles nevertheless extend to general linear PBE solvers. The 3D linear PBE model can also be used to benchmark and validate the salt effect prediction capabilities of existing PBE solvers. This choice promises to be particularly useful in the context of biological applications where the solvation energy, arising from medium polarization, has a prime role.

1. Introduction

Electrostatic interactions are important factors in determining the native structures of both proteins and nucleic acids as well as their complexes with low-molecular-weight drugs [1,2,3]. The longrange nature of electrostatic interactions, even in aqueous solution, is one reason why its theoretical treatment is difficult. In order to circumvent the considerable and often prohibitive computational expense of microscopic (explicit) solvent models which, in principle, afford an exact treatment of electrostatic interactions in solution, there has been much renewed interest in the use of simpler continuum models [1–9]. In one class of continuum models [5–9] the explicit structural features of the solvent are replaced by a linear high dielectric constant continuum surrounding the solute, which is modeled as a low dielectric constant charge-containing cavity. For ionic solutions, the ion distribution is modeled as a mean field, determined from statistical mechanics according to a Boltzmann distribution. The solute charge distribution and, at nonzero ionic strength, the mobile ion distribution polarize the solvent, giving rise to a solvent reaction potential. The calculation of the polarization of the solvent is carried out by solving the Poisson equation or, when ionic strength effects are to be included, by solving the more general Poisson–Boltzmann (PB) equation.

The interaction of the solvent reaction potential with the solute charge distribution determines the free energy of solvation of the system. Although very simple, such continuum models have been

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useful for making predictions concerning electrostatic effects in proteins [10–13] which show reasonable agreement with experimental observations. A set of very elegant calculations has recently shown that continuum models reproduce solute-solvent free energies obtained by using a microscopic treatment of the solvent [37]. It is likely that the success of such continuum models is in part due to cancellation effects in the behavior of water at the molecular level [14,15]. The use of such continuum models is especially suitable for aqueous systems because of the unique behavior of the local dielectric constant in the region of the dielectric boundary. At the boundary, the dielectric constant varies very rapidly over a microscopic distance to the value of the dielectric constant for bulk water. This is consistent with the assumption in the continuum model that there are only two (discontinuous) dielectrics separated by a molecular interface. In addition, calculations of the potential of mean force between ions in aqueous solution using integral equation theories [16] have shown that water completely screens vacuum Coulombic interactions within one hydration shell.

Such behavior is well represented by simple continuum models. Analytical solutions of the PB equation can be obtained for only a very few, simple cavity shapes. Hence, in order to study macromolecular systems in aqueous ionic solution using cavity-based continuum models, efficient methods for obtaining approximate numerical solutions to the PB equation have been developed, although some drawbacks remain with each method. There are broadly two different approaches in seeking approximate numerical solutions of the PB equation. One such approach is the finite difference (FD) method, first used to study bio-macromolecular systems by Warwicker and Watson [5], with several very important algorithmic advances being added later by Gilson et al. [6] and Nicholls and Honig [18]. The finite-difference method is very general and has been used to obtain solutions of the full nonlinear Poisson–Boltzmann (NLPB) equation [19]. In this method, the solute and solvent are mapped onto a cubic lattice. Each of small cubes defining the lattice is assigned an appropriate value of the charge density, dielectric constant, and ionic strength parameters that appear in the PB equation. The method of finite-differences is then used to obtain the electrostatic potential over the entire grid iteratively. This technique involves N^3 variables (the total number of lattice sites), where N is the number of points per edge of the lattice. There are some difficulties encountered when using finite-difference techniques. One concerns the necessary choice of boundary conditions. These can be obtained at sufficiently large distance with respect to the dielectric boundary from either Coulomb's law or Debye-Hückel theory. To achieve a high degree of accuracy, it is necessary to consider the continuum solvent that is far from the solute; this entails increasing the lattice size (relative to the molecule) and hence the expense of the calculation. A second problem associated with the finite-difference technique arises because of the necessity to map the molecular charge distribution onto lattice points. The resulting error arising from this disturbance of the optimal charge distribution is a function of the lattice spacing (although it is in general small). However, when the molecular charge distribution is approximated by a set of distributed multipoles, it is clearly that mapping onto the lattice would have to be achieved by using a limiting monopole distribution. Faerman and Price [20] have recently demonstrated the utility of using such a distributed multipole description to obtain very accurate descriptions of the electrostatic field/potential at the molecular surface, for peptide molecules, a prerequisite for the success of electrostatic continuum solvent models. An alternative approach for obtaining solutions of the Poisson equation is the boundary element method, first developed for macromolecules by Zauhar and Morgan [21], with different algorithmic improvements proposed by Rashin and Namboodiri [9] and Zauhar and Morgan [21,22,59].

The key feature of the boundary element method is the reduction of the problem to the solution of an integral equation over a two-dimensional surface. The polarization of the solvent by the solute induces a field throughout the volume of the surrounding dielectric medium. Calculation of the polarization field is equivalent to the calculation of induced polarization charge density at the dielectric boundary [7,23].

The boundary element method is a function of S independent variables, where S is the number of elements covering the two-dimensional surface, which serves as the dielectric interface. There is no requirement to displace atomic charge distributions when using this method, and in general the method allows for a more accurate description of the molecular surface than the finite-difference method. The boundary element method has thus far been used to calculate the total electrostatic potential and the associated electrostatic component of the free energy of solvation [7,9]. Rashin [24] has described a combined iterative boundary element method to obtain solutions of the general PB equation, but has not presented details for carrying out accurate volume integrations, or about the convergence properties of the scheme. The inclusion of ionic strength effects in continuum models is often achieved by using a linearized version of the Poisson–Boltzmann equation [1,17,25,26]. Unlike the full nonlinear version, the linear Poisson–Boltzmann (LPB) equation is formally correct in the limit of low ionic strength and can be derived within a statistical mechanical framework from a partition function [26]. However, use of the LPB equation is unlikely to be suitable for all investigations concerning macromolecular structure. This is because, even at low ionic strength, the main condition for linearization, i.e., $.q_i\phi(r)/kT < 1$.(where $\phi(r)$ is the electrostatic potential, q_i is the ion charge, T is temperature, and k is the Boltzmann constant), appears to break down at room temperature in aqueous solution if the distance between an ion and an exposed polar atom is smaller than 5 Å, according to our calculations. The ion charge density predicted by the LPB equation is generally too low and leads to incorrect estimations of ion screening between charged atoms. A detailed discussion concerning the validity of the NLPB equation, as well as derivations of various forms of the associated total electrostatic energy, has been given recently by Sharp and Honig [27].

The purpose of the present paper is to develop a procedure to obtain solutions to the NLPB equation within the framework of the previously described boundary element method. The underlying physical basis of our method is our observation that, at relatively low ionic strength ($\leq$1 M), the distribution of mobile ions around the solute molecule is determined primarily by the potential due to the solute charge distribution and the reaction solvent potential (viz. the potential due to the surface charges obtained in the boundary element method). This makes possible the calculation of the mobile ion distribution around the molecule in a way that the polarization of the solvent by the solute charge distribution is calculated by using a boundary element method. The accuracy of the results obtained by using the boundary element method (BEM) is tested by comparison with analytical Tanford–Kirkwood results for a model spherical solute system. Finally, the author also consider how the general ion exclusion layers tend to increase the surface electrostatic potential under physiological salt conditions. To facilitate presentation and computational domain, attention is restricted here to the 3D spherically symmetric linear PBE. Though geometrically limited, the modeling principles nevertheless extend to general linear PBE solvers. The 3D linear PBE model can also be used to benchmark and validate the salt effect prediction capabilities of existing PBE solvers.