

## Poisson-Boltzmann Calculations: van der Waals or Molecular Surface?

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**Abstract.** The Poisson-Boltzmann equation is widely used for modeling the electrostatics of biomolecules, but the calculation results are sensitive to the choice of the boundary between the low solute dielectric and the high solvent dielectric. The default choice for the dielectric boundary has been the molecular surface, but the use of the van der Waals surface has also been advocated. Here we review recent studies in which the two choices are tested against experimental results and explicit-solvent calculations. The assignment of the solvent high dielectric constant to interstitial voids in the solute is often used as a criticism against the van der Waals surface. However, this assignment may not be as unrealistic as previously thought, since hydrogen exchange and other NMR experiments have firmly established that all interior parts of proteins are transiently accessible to the solvent.

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**Key words:** Poisson-Boltzmann calculation, biomolecular electrostatics, dielectric boundary, van der Waals surface, molecular surface.

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## 1 Introduction

Electrostatics plays important roles in biomolecular interactions, such as between proteins, ligands, and nucleic acids [1–3]. Stability, specificity, and rates can all be tuned by charge mutations. The development of reliable and fast methods for computing electrostatic free energies has attracted great attention in the past several decades. The Poisson-Boltzmann (PB) equation has emerged as one of the most widely used method for modeling biomolecular electrostatics. Advances and biophysical applications of the PB model can be found in many recent reviews [4–10]. One particular aspect of the PB model is

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that calculation results are very sensitive to the specification of the boundary between the low dielectric solute and the high dielectric solvent [11–19]. What is the proper dielectric boundary in PB calculations is still an open question. The present review focuses on recent studies addressing this question.

## 2 Solvation energy

The energy of a biomolecule (or a biomolecular complex) in an aqueous environment can be decomposed into an internal component and a solvation component. The solvation energy is determined by the interactions of the solute molecule and the solvent molecules (water, ions, and other species). Operationally the solvation energy is the free energy of transferring the solute molecule from a reference medium to the aqueous environment. Solvation energy can be calculated by a variety of methods, from the very time-consuming quantum mechanical approaches to simple Coulomb's law [20, 21]. Broadly speaking there are two types of solvation models: explicit solvent and implicit solvent. The explicit models represent the solvent in molecular and atomic details, and therefore require extensive computational sampling and provide a physically more sound description. In contrast, implicit solvent models represent the solvent as a dielectric continuum; the calculation is more efficient and the results are usually more intuitive to interpret.

## 3 Poisson-Boltzmann equation

The most popular implicit solvation model is based on the PB. It is a second-order elliptic partial differential equation describing the electrostatic potential around a fixed charge distribution in an ionic solution. The full, nonlinear PB equation in a solution containing a 1:1 salt takes the form

$$\nabla \cdot \varepsilon(\mathbf{r}) \nabla \phi(\mathbf{r}) = (\varepsilon_s k_B T / e) \kappa^2 S(\mathbf{r}) \sinh[e\phi(\mathbf{r}) / k_B T] - 4\pi\rho(\mathbf{r}),$$

where  $\phi(\mathbf{r})$  is the electrostatic potential at position  $\mathbf{r}$ ;  $\varepsilon(\mathbf{r})$  denotes the dielectric constant, with value  $\varepsilon_p$  in the solute dielectric and  $\varepsilon_s$  in the solvent dielectric;  $\kappa$  is the Debye-Hückel screening parameter dependent on the ionic strength of solution;  $S(\mathbf{r})$  is a "masking" function with value 1 in the region accessible to the ions in the solvent and value 0 elsewhere;  $e$  is the protonic charge;  $k_B$  is Boltzmann's constant;  $T$  is the absolute temperature; and  $\rho(\mathbf{r})$  is the solute charge density. Expanding  $\sinh[e\phi(\mathbf{r}) / k_B T] \equiv \sinh\tilde{\phi}(\mathbf{r})$  to the lowest order results in the linearized PB equation:

$$\nabla \cdot \varepsilon(\mathbf{r}) \nabla \phi(\mathbf{r}) = \varepsilon_s \kappa^2 S(\mathbf{r}) \phi(\mathbf{r}) - 4\pi\rho(\mathbf{r}).$$

The electrostatic free energy of the system is [22]

$$G_{\text{el}} = \int d^3\mathbf{r} \left\{ \frac{1}{2} \rho(\mathbf{r}) \phi(\mathbf{r}) + \frac{\varepsilon_s (k_B T \kappa / e)^2}{4\pi} S(\mathbf{r}) \left[ 1 + \frac{1}{2} \tilde{\phi}(\mathbf{r}) \sinh\tilde{\phi}(\mathbf{r}) - \cosh\tilde{\phi}(\mathbf{r}) \right] \right\}.$$