

# A Modified Nonlocal Continuum Electrostatic Model for Protein in Water and Its Analytical Solutions for Ionic Born Models

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**Abstract.** A nonlocal continuum electrostatic model, defined as integro-differential equations, can significantly improve the classic Poisson dielectric model, but is too costly to be applied to large protein simulations. To sharply reduce the model's complexity, a modified nonlocal continuum electrostatic model is presented in this paper for a protein immersed in water solvent, and then transformed equivalently as a system of partial differential equations. By using this new differential equation system, analytical solutions are derived for three different nonlocal ionic Born models, where a monoatomic ion is treated as a dielectric continuum ball with point charge either in the center or uniformly distributed on the surface of the ball. These solutions are analytically verified to satisfy the original integro-differential equations, thereby, validating the new differential equation system.

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## 1 Introduction

Continuum electrostatic models play an important role in the study and simulation of protein functions and protein-ligand relations [21, 27]. Based on both classical and quantum mechanical approaches, they have been well developed in terms of the Poisson and Poisson-Boltzmann equations, and have been widely applied to the calculation of electrostatic potential energy for protein simulations in both water and ionic solvent environments [1, 7, 10, 17, 22, 24, 28]. In these models, water is simply treated as a featureless

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continuum medium with a dielectric constant; an important structural feature — the polarization correlations among water molecules — is totally ignored.

To develop more sophisticated continuum electrostatic models that reflect this structural feature of water, an approach called “nonlocal electrostatics” has been studied in literature [2–6, 18–20, 26, 29]. In this approach, the dielectric constant of water is replaced by a dielectric function  $\epsilon(\mathbf{r}, \mathbf{r}')$  of two space variables  $\mathbf{r}$  and  $\mathbf{r}'$  such that the linear response relation of the displacement field  $\mathbf{d}(\mathbf{r})$  with the electric field  $\mathbf{e}(\mathbf{r})$ , which is defined as  $\nabla\Phi(\mathbf{r})$ , is extended as a triple integral over the water range domain  $D_s$ :

$$\mathbf{d}(\mathbf{r}) = \epsilon_0 \int_{D_s} \epsilon(\mathbf{r}, \mathbf{r}') \nabla\Phi(\mathbf{r}') d\mathbf{r}', \quad \mathbf{r} \in D_s, \quad (1.1)$$

where  $\Phi(\mathbf{r})$  denotes the electrostatic potential density function. The classic Poisson dielectric model is then extended as a nonlocal continuum electrostatic model. As defined in integro-differential equations, however, the nonlocal model is too costly to be solved numerically for a large protein simulation problem. One strategy to sharply reduce the cost of solving a nonlocal model is to reformulate the nonlocal model as a set of differential equations. This strategy has been adopted by several authors, yielding some numerical algorithms and program packages for solving nonlocal models [9, 13, 15, 23, 30, 32].

We observed that the complexity of a nonlocal model can be sharply reduced, provided that the gradient operator  $\nabla$  is taken out of the integration [32]. Since the domain  $D_s$  of integration may have a complicated geometry, such a switch of the gradient operator with the integral operator may produce either mathematical uncertainty or computational difficulties (e.g., using Green’s formula results in a surface integral over the interface  $\Gamma$  between the protein and water ranges, which is difficult to compute since  $\Gamma$  is a molecular surface of the protein). To avoid such potential obstacles, in this paper, we simply modify the relation (1.1) by setting the domain of integration as the whole space  $\mathbb{R}^3$ . Such a modification is reasonable since each water molecule is also subject to the polarization correlations from all other charged atoms/ions outside the water range domain  $D_s$ . Using this modified integral of (1.1), we derive a modified nonlocal continuum electrostatic model, in which the integral terms can be expressed in terms of convolution. Using the properties of convolution, we then rigorously transform the modified nonlocal model equivalently from the integro-differential equations into a system of partial differential equations, along with proper jump conditions on the interface between the water and protein ranges. Our differential formulation is different from the one given in [13, 15].

To validate our differential formulation, we use the new differential equation system to calculate the analytical solutions of two typical nonlocal ionic Born models, called the nonlocal point charge Born model and the nonlocal spherical shell Born model. In these models, a monoatomic ion is treated as a dielectric continuum ball with point charge in the center or uniformly distributed on the surface of the ball, respectively. We also find the analytical solution of a traditional nonlocal point charge Born model defined in [13, 15] based on our approach. Furthermore, by direct calculation of convolution, we verify that these analytical solutions satisfy their original integro-differential equations.