A Nonlocal Poisson-Fermi Model for Ionic Solvent

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We propose a nonlocal Poisson-Fermi model for ionic solvent that includes ion size effects and polarization correlations among water molecules in the calculation of electrostatic potential. It includes the previous Poisson-Fermi models as special cases, and its solution is the convolution of a solution of the corresponding nonlocal Poisson dielectric model with a Yukawa-type kernel function. Moreover, the Fermi distribution is shown to be a set of optimal ionic concentration functions in the sense of minimizing an electrostatic potential free energy. Finally, numerical results are reported to show the difference between a Poisson-Fermi solution and a corresponding Poisson solution.

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I. INTRODUCTION

Ionic solutions have been studied for a very long time, usually by using the Poisson-Boltzmann equation (PBE) as a starting point. The PBE model has its successes [2–4, 14, 26, 31, 37, 49, 64, 75, 76], particularly compared to the treatment of ionic solutions by the theory of ideal (uncharged) perfect gases, found in biochemistry texts [74, 79]. But the successes of PBE are mostly qualitative because sodium and potassium ions are not the same (for example). Real ionic solutions have nonideal excess properties [23, 46] that distinguish between types of ions (e.g., sodium and potassium) that cannot be approximated by PBE treatments in which sodium and potassium are identical point charges. The different specific properties of ions are of the greatest importance in biology and technology [18, 21–25, 32, 39, 43–47, 60–62, 64, 79] As Nobelist Aaron Klug (over-) states the issue [36]: "There is only one word that matters in biology, and that is specificity." Both life and electrochemical technology (e.g., batteries) depend on the difference between ions. If your nerve cells lose their ability to deal separately with sodium and potassium ions, you die, in minutes.

The need for more realistic theories was well known in physical chemistry nearly a century ago and the failure to make much progress has been a source of great frustration. For example, a leading monograph, in print for more than fifty years, says "... many workers adopt a counsel of despair, confining their interest to concentrations below about 0.02 M ..." [65, page 302], an opinion restated in even more colorful language by up-to-date references as well: "It is still a fact that over the last decades, it was easier to fly to the moon than to describe the free energy of even the simplest salt solutions beyond a concentration of 0.1M or so" [44, page 10]. These issues are discussed, and some of the innumerable references are listed in [5, 6, 10, 17–21, 23–25, 33, 39, 43–47, 61, 62, 65, 78, 90]. The nonideal properties of ionic solutions arise because ions are not points of charge. Rather, ions are charged molecules that also can interact with the highly polar solvent water. Water has a complex distribution of charge, with zero net charge but significant local centers of charge. Much of biology depends on the properties of spherical ions that have charge independent of the local electric field (sodium and potassium ions) or are customarily treated (with reasonable success) as if they have charge independent of the local electric field (chloride and calcium ions). These bio-ions — as they might be called because of their enormous significance to biology (documented in the classical texts of physiology and biophysics [12, 38, 68]) — have nonideal properties mostly because they are spheres not points and solutions made of spheres have entropy and energy quite different from solutions of points. Bio-ions have their greatest importance where they are most concentrated, in and near the electrodes of batteries and electrochemical cells, in and near ion channel proteins, ion binding proteins (including drug receptors), nucleic acids (DNA and RNA of various types), and enzymes, particularly their active sites [34]. Where they are most impor-

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tant, ion concentrations are usually more than 10 molar, often reaching 100 molar (!), more concentrated than table salt Na^+Cl^- (37 molar). This surprising fact is the subject of the reviews [10, 17, 25], and is documented there for L-type calcium channels, DEKA sodium channels, and ryanodine receptor channels. Similar charge densities are found in catalytic active sites [34] and in Rb^+ binding sites in the KcsA potassium channel [60].

In the last decades, simple treatments of ionic solutions as spheres of fixed charge in a dielectric have had surprising success in describing detailed properties of complex systems, including bulk solutions [10, 17, 25, 57, 58] and ion channels, starting with approximate treatments of bulk solutions, moving to Monte Carlo simulations of all sphere systems, culminating in a variational treatment [22] that combines diffusion, migration, and convection using the energetic variational approach pioneered by Chun Liu [51, 70] more than anyone else.

The variational treatment, however, computes forces between all spheres and so leads to partial differential equations that are difficult to solve even numerically in three dimensions. Spheres cannot overfill space and the resulting saturation phenomena can be dealt with by the Fermi-like distribution derived by Jinn-Liang Liu [52], which was then used by Liu and Eisenberg to compute the entropy of an arbitrary mixture of spheres of any diameter in various systems [53–55, 57, 58]. This Fermi-like approach describes bulk ionic solutions, calcium channels, and the gramicidin channel (in a model based on its three dimensional structure) with some success but it is based on an approximate treatment of the energy and free energy of these systems using Santangelo's potential model [72] that has been popularized by [9] and others [77].

Santangelo's model neatly encloses the near-field correlations in a far field Poisson equation and boundary conditions that allow flow when combined with a diffusion (Nernst-Planck) representation. The separation of near and far fields depends on a single screening parameter, however, and this is clearly an over-simplification, perhaps with significant limitations, particularly in the crowded situations where ions are most important. In reality, the screening includes both solvent and solute effects, neither of which can be captured by a single parameter independent of ion concentration and type. Rather, the screening effects of other ions depend on concentration, even in the (nearly) ideal case of point charged ions, and on the diameter of ions and the composition of their solution in general. In addition, the attenuation by dielectric properties of the solvent — that might be called dielectric screening as described by the Bjerrum constant — must be nonlocal, because the water molecules that make up the solvent are connected by a chain of hydrogen bonds. A replacement of Santangelo's model that is nonlocal is needed, and that is what we provide here.

The study of nonlocal dielectric continuum models was started thirty years ago to account for either the polarization correlations among water molecules or the spatial-frequency dependence of a dielectric medium in the prediction of electrostatics [8, 11, 13, 16, 41, 66, 71, 73]. Because of the complexity and difficulty in numerical solution, early work was done only on a Lorentz nonlocal model for the water solvent with charges near a half-space or a dielectric sphere containing one central charge or multiple charges [7, 42, 67, 80]. To sharply reduce the numerical complexity, Hildebrandt *et al.* developed novel reformulation techniques to modify the Lorentz nonlocal model into a system of two coupled partial differential equations (PDEs) [30], opening a way to solve a nonlocal model numerically by advanced PDE numerical techniques [29, 81]. Motivated by Hildebrandt *et al.*'s work, Xie *et al.* adopted different reformation techniques than the ones used by Hildebrandt *et al.* to reformulate the Lorentz nonlocal model for water into two decoupled PDEs, and solved them by a fast finite element algorithm [84]. Their reformulation techniques were then applied to the construction of a new nonlocal dielectric model for protein in water [87] and a general nonlocal Poisson dielectric model for protein in ionic solvent [83, 85]. In fact, this general nonlocal Poisson dielectric model is the first ionic solvent model that incorporates nonlocal dielectric effects in the field of dielectric continuum modeling. It also provides us with a general framework for developing various nonlocal dielectric models. As one of its applications, a nonlocal modified Poisson-Boltzmann equation (NMPBE) has recently been derived as part of a nonlinear nonlinear and nonlocal dielectric continuum model for protein in ionic solvent [83].

However, none of the current ionic models incorporate both nonlocal dielectric effects and ionic size effects due to modeling and algorithmic challenges. As the first step toward the direction of changing this situation, in this paper, we propose a nonlocal Poisson-Fermi dielectric model for ionic solution. We generalize Santangelo's model as a nonlocal Poisson-Fermi model to reflect both the spatial frequency of dielectric and ionic size effects in the calculation of electrostatics for an ionic solvent containing multiple ionic species.

In particular, we show in this paper that our nonlocal Poisson-Fermi model includes Santangelo's model as a special case, and its solution is nothing but a convolution of the solution of a nonlocal Poisson dielectric model with a Yukawa-like kernel function, which is commonly used in the construction of a nonlocal dielectric model. Furthermore, we extend the Fermi-like distribution derived by Liu and Eisenberg, and prove it to be optimal in the sense of minimizing an electrostatic free energy functional. In fact, one significant feature of Liu's Fermi-Poisson treatment [56, eq. (10)] is to model interstitial voids as a particle species. However, the size of each void is position-dependent, which is difficult to deal with in the derivation of a Fermi-like distribution. Such a difficulty has been avoided in our new Fermi-like distribution, which only requires the bulk concentrations of ions and water molecules and the radii of ions and water molecules, due to our modification on the traditional

electrostatic free energy functional used in the PBE study (see [50, 59] for example).

Our new Poisson-Fermi model turns out to be a system of $n+2$ nonlinear equations — one fourth order elliptic partial differential equation for defining an electrostatic potential function and $n+1$ nonlinear algebraic equations for the concentration functions of n ionic species and water molecules. Its numerical solution raises a challenge in computational mathematics and high performance scientific computing particularly when confined spaces must be described by jump boundary conditions, as in ion channels with discontinuities of dielectric properties and coefficients. It will be studied in our sequential papers. In this paper, we only report numerical results on a simple nonlocal Poisson test model, whose analytical solution was given in Xie *et al.*'s recent work [88] as well as its convolution for a dielectric ball containing multiple charges, since our purpose is to illustrate one major difference between the solutions of the Poisson-Fermi and Poisson models. Here, the convolution of the solution was done with the same Yukawa-like kernel function as the one used in our nonlocal Poisson-Fermi model; thus, it can be regarded as a solution of a Poisson-Fermi model even without any consideration of ionic size effects. The comparison tests were done by using 488 point charges coming from a protein molecule (PDB ID: 2XLZ). The numerical results demonstrate that the Poisson-Fermi model can have a much smoother solution and a much smaller solution range than the corresponding Poisson dielectric model. Consequently, from a sufficient condition that we obtain to guarantees a well defined Poisson-Femi model it implies that the Poisson-Fermi model can be much more stable numerically than the Poisson dielectric model in the calculation of ion concentrations.

We organize the remaining part of the paper as follows. In Section II, we review the nonlocal Poisson dielectric model. In Section III, we present the new nonlocal Poisson-Fermi model. In Section IV, we derive the new nonlocal Fermi distribution. In Section V, we present a dimensionless nonlocal Poisson-Fermi model, and a sufficient condition to ensure its definition. In Section VI, we discuss one numerical stability issue related in ionic concentration calculation. The conclusions are made in Section VII.

II. A NONLOCAL POISSON DIELECTRIC MODEL

We start with a short review on the derivation of a nonlocal Poisson dielectric model. Let $\mathbf{e}$ denote an electrostatic field. When a fixed charge density function ρ and a polarization charge density function γ are given, $\mathbf{e}$ can be simply defined by Gauss's law as follows:

$$\epsilon_0 \nabla\cdot\mathbf{e}(\mathbf{r}) = \gamma(\mathbf{r}) + \rho(\mathbf{r}) \quad \text{for } \mathbf{r} = (x_1, x_2, x_3) \in \mathbb{R}^3, \quad (1)$$

where ϵ_0 is the permittivity of the vacuum. However, it is difficult to obtain γ in practice. To avoid the difficulty, the classic linear dielectric theory [15, 27] has been established based on the linear relationships of displacement field $\mathbf{d}$ and polarization field $\mathbf{p}$ with $\mathbf{e}$:

$$\text{(a)} \quad \mathbf{d}(\mathbf{r}) = \epsilon_0 \varepsilon(\mathbf{r})\mathbf{e}(\mathbf{r}); \quad \text{(b)} \quad \mathbf{p}(\mathbf{r}) = \epsilon_0 \chi(\mathbf{r})\mathbf{e}(\mathbf{r}), \quad (2)$$

where $\mathbf{d}$ and $\mathbf{p}$ are defined by

$$\text{(a)} \quad \nabla\cdot\mathbf{d}(\mathbf{r}) = \rho(\mathbf{r}); \quad \text{(b)} \quad -\nabla\cdot\mathbf{p}(\mathbf{r}) = \gamma(\mathbf{r}), \quad (3)$$

ε is the permittivity function, and χ is the susceptibility function. Since $\mathbf{e}$ is conservative, there exists an electrostatic potential function, Φ, such that

$$\mathbf{e}(\mathbf{r}) = -\nabla\Phi(\mathbf{r}). \quad (4)$$

Hence, applying the above formula and (2a) to (3a), we obtain the classic Poisson dielectric model:

$$-\epsilon_0\nabla\cdot(\varepsilon(\mathbf{r})\nabla\Phi(\mathbf{r})) = \rho(\mathbf{r}) \quad \forall \mathbf{r} \in \mathbb{R}^3, \quad (5)$$

where $\Phi(\mathbf{r}) \to 0$ as $|\mathbf{r}| \to \infty$, and $\Delta = \sum_{i=1}^3 \frac{\partial^2}{\partial x_i^2}$ is the Laplace operator.

It has been known that the relationship (2) depends on a spatial frequency of a dielectric medium (see [35] for example). To reflect this feature, the spatial frequency variable of the Fourier transform can be employed to model the spatial frequency dependence of the dielectric response, so that the two linear relationships of (2) can be mimicked in the Fourier frequency space as follows:

$$\text{(a)} \quad \widehat{\mathbf{d}}(\xi) = \epsilon_0 \widehat{\varepsilon}(\xi)\widehat{\mathbf{e}}(\xi); \quad \text{(b)} \quad \widehat{\mathbf{p}}(\xi) = \epsilon_0 \widehat{\chi}(\xi)\widehat{\mathbf{e}}(\xi), \quad (6)$$

where $\widehat{\varepsilon}(\xi), \widehat{\chi}(\xi), \widehat{\mathbf{d}}(\xi), \widehat{\mathbf{p}}(\xi)$, and $\widehat{\mathbf{e}}(\xi)$ denote the Fourier transforms of $\varepsilon(\mathbf{r}), \chi(\mathbf{r}), \mathbf{d}(\mathbf{r})$, $\mathbf{p}(\mathbf{r})$, and $\mathbf{e}(\mathbf{r})$, respectively [8]. Applying the inverse Fourier transform to (6), we obtain the nonlocal relationships of $\mathbf{d}$ and $\mathbf{p}$ with $\mathbf{e}$:

$$\mathbf{d}(\mathbf{r}) = \epsilon_0 \int_{\mathbb{R}^3} \varepsilon(\mathbf{r}-\mathbf{r}')\mathbf{e}(\mathbf{r}')\, d\mathbf{r}', \quad (7a)$$

$$\mathbf{p}(\mathbf{r}) = \epsilon_0 \int_{\mathbb{R}^3} \chi(\mathbf{r}-\mathbf{r}')\mathbf{e}(\mathbf{r}')\, d\mathbf{r}'. \quad (7b)$$

Substituting (7a) and (4) to (3a), we obtain the nonlocal Poisson dielectric model:

$$-\epsilon_0\nabla\cdot\int_{\mathbb{R}^3} \varepsilon(\mathbf{r}-\mathbf{r}')\nabla\Phi(\mathbf{r}')\, d\mathbf{r}' = \rho(\mathbf{r}) \quad \forall \mathbf{r} \in \mathbb{R}^3, \quad (8)$$

where $\Phi(\mathbf{r}) \to 0$ as $|\mathbf{r}| \to \infty$. In particular, following Debye's (temporal) frequency dependent permittivity function (see [8, page 100] and [35] for example), we set $\widehat{\varepsilon}$ in the expression

$$\widehat{\varepsilon}(\xi) = \epsilon_\infty + \frac{\epsilon_s - \epsilon_\infty}{1 + \lambda^2|\xi|^2}, \quad (9)$$

where ε_s and ε_∞ are the static and optic values corresponding to the spatial frequencies $|\xi| = 0$ and $|\xi| \to \infty$,

respectively, $\epsilon_s > \epsilon_\infty$, and λ is a parameter for characterizing the spatial frequency of the water solvent as a dielectric medium (or the polarization correlations of water molecules) [28, 89]. The inverse Fourier transform of $\widehat{\varepsilon}$ gives the commonly-used nonlocal permittivity function

$$\varepsilon(\mathbf{r}) = \epsilon_\infty \delta(\mathbf{r}) + (\epsilon_s - \epsilon_\infty) Q_\lambda(\mathbf{r}) \quad \forall \mathbf{r} \in \mathbb{R}^3, \tag{10}$$

where δ denotes the Dirac-delta distribution at the origin [69], and Q_λ is given by

$$Q_\lambda(\mathbf{r}) = \frac{e^{-|\mathbf{r}|/\lambda}}{4\pi\lambda^2|\mathbf{r}|}.$$

Applying (10) to (8), we obtain the nonlocal Poisson dielectric model: For $\mathbf{r} \in \mathbb{R}^3$,

$$-\epsilon_0 \left[\epsilon_\infty \Delta\Phi(\mathbf{r}) + (\epsilon_s - \epsilon_\infty)\nabla\cdot(\nabla\Phi * Q_\lambda)(\mathbf{r})\right] = \rho(\mathbf{r}), \tag{11}$$

where $\Phi(\mathbf{r}) \to 0$ as $|\mathbf{r}| \to \infty$, and $\nabla\Phi * Q_\lambda$ denotes the convolution of $\nabla\Phi$ with O_λ, which is defined by

$$(\nabla\Phi * Q_\lambda)(\mathbf{r}) = \int_{\mathbb{R}^3} Q_\lambda(\mathbf{r} - \mathbf{r}')\nabla\Phi(\mathbf{r}')\mathrm{d}\mathbf{r}'.$$

Furthermore, by the derivative properties of the convolution [69, Theorem 6.30, Page 171], the nonlocal Poisson dielectric model (11) can be reformulated in the form

$$-\epsilon_0 \Delta \left[\epsilon_\infty \Phi + (\epsilon_s - \epsilon_\infty)(\Phi * Q_\lambda)\right] = \rho(\mathbf{r}), \ \mathbf{r} \in \mathbb{R}^3. \tag{12}$$

One interesting issue on the study of the nonlocal Poisson dielectric model comes from the selection of parameter λ. Many studies were done for different ionic solvents and different applications (see [5, 32, 39, 63, 90], [84, Figure 2.1], and [28, 29] for example), showing that a value of λ can vary from 3 to 25.

While a value of λ can be selected experimentally, it can also be estimated theoretically by a formula to yield a reference value for experiments. To get such a formula, we rewrite Q_λ as

$$Q_\lambda(\mathbf{r}) = \frac{1}{\lambda^2} H(\mathbf{r}) \quad \forall \mathbf{r} \in \mathbb{R}^3 \quad \text{with} \quad H = \frac{e^{-|\mathbf{r}|/\lambda}}{4\pi|\mathbf{r}|},$$

where H is the Yukawa kernel function [40], which satisfies the distribution equation

$$-\Delta H(\mathbf{r}) + \frac{1}{\lambda^2} H(\mathbf{r}) = \delta(\mathbf{r}), \quad \mathbf{r} \in \mathbb{R}^3. \tag{13}$$

We recall that a Debye-Hückel equation for a symmetric 1:1 ionic solvent is defined by

$$-\epsilon_s \Delta u(\mathbf{r}) + \kappa^2 u(\mathbf{r}) = \frac{10^{10} e_c^2}{\epsilon_0 k_B T} z\delta(\mathbf{r}), \quad \mathbf{r} \in \mathbb{R}^3, \tag{14}$$

where k_B is the Boltzmann constant, T is the absolute temperature, e_c is the elementary charge, z is the charge number at the origin, and κ is given by

$$\kappa = \frac{e_c}{10^8\sqrt{5}} \left(\frac{N_A I_s}{\epsilon_0 k_B T}\right)^{1/2} \tag{15}$$

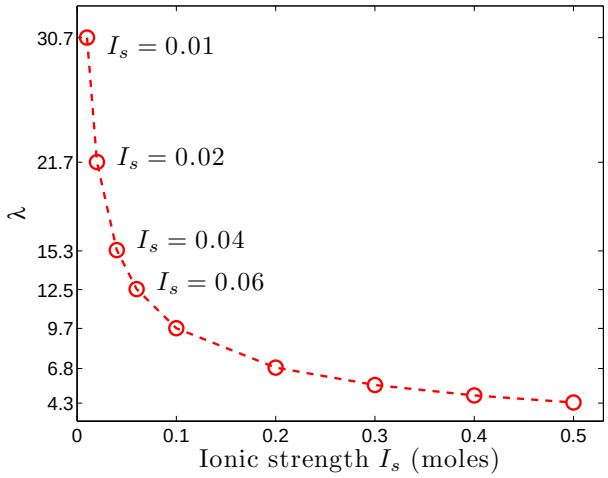

FIG. 1: The correlation length parameter λ predicted by formula (16) as a decreasing function of I_s.

with N_A being the Avogadro number ($N_A = 6.02214129 \times 10^{23}$) and I_s the ionic solvent strength. Clearly, the Debye-Hückel equation is reduced to (13) in the case that $z = \epsilon_0\epsilon_s k_B T/(10^{10} e_c^2)$, and $\lambda = \sqrt{\epsilon_s}/\kappa$, from which we obtain a formula for estimating λ:

$$\lambda = \frac{10^8\sqrt{5}}{e_c} \left(\frac{\epsilon_0\epsilon_s k_B T}{N_A I_s}\right)^{1/2}. \tag{16}$$

Here λ has the length unit in angstroms (Å) since (14) is in the dimensionless form produced by using the length unit in angstroms under the SI unit system.

By the formula (16) with the parameter values of k_B, e_c, ϵ_0 and T given in [82, Table 1], λ was found to have the range $4.3 \le \lambda \le 30.7$ for $0.01 \le I_s \le 0.5$ as displayed in Figure 1. Further studies will be done on a proper selection of λ in our sequential work.

III. THE NONLOCAL POISSON-FERMI MODEL

In this section, we derive a nonlocal Poisson-Fermi model for computing the convolution of Φ with respect to the Yukawa-like kernel function Q_λ. We then show that the electrostatic potential Φ can be split into two component functions — one for permittivity correlations among water molecules and the other one for ionic size effects.

Doing the convolution of Φ on the both sides of (13), we find that Φ can be expressed in the form

$$\Phi(\mathbf{r}) = -\lambda^2 \Delta W(\mathbf{r}) + W(\mathbf{r}), \quad \mathbf{r} \in R^3, \tag{17}$$

where we have set $W = \Phi * Q_\lambda$, and used the derivative identity $\Phi * \Delta Q_\lambda = \Delta(\Phi * Q_\lambda)$. The above expression can lead to a new way for us to calculate the electrostatic potential function Φ provided that we can construct an equation for W to calculate both W and $\Delta W(\mathbf{r})$ quickly.

In general, the convolution $\Phi * Q_\lambda$ can be much more smooth than Φ without involving any singularity over the whole space $\mathbb{R}^3$. For example, Figure 2 shows that the convolution $\Phi * Q_\lambda$ has smoothed a strongly singular Φ, and sharply reduced the range of Φ. Hence, an equation for W should be much easier to solve numerically and should give a much more accurate numerical solution than the equation of Φ.

We now produce an equation for W from the nonlocal dielectric model (12). With (17), we can reformulate the expression $\epsilon_\infty\Phi + (\epsilon_s - \epsilon_\infty)(\Phi * Q_\lambda)$ in terms of W as follows:

$$\epsilon_\infty\Phi + (\epsilon_s - \epsilon_\infty)(\Phi * Q_\lambda) = \epsilon_s W - \epsilon_\infty\lambda^2\Delta W.$$

Let $l_c^2 = \frac{\epsilon_\infty}{\epsilon_s}\lambda^2$. Applying the above expression to the nonlocal model (12) yields an equation for W as follows:

$$-\epsilon_0\epsilon_s\Delta\left[W(\mathbf{r}) - l_c^2\Delta W(\mathbf{r})\right] = \rho(\mathbf{r}), \quad \mathbf{r}\in\mathbb{R}^3, \tag{18}$$

where $W \to 0$ and $\Delta W \to 0$ as $|\mathbf{r}| \to \infty$, which can be followed from (17) and $\Phi \to 0$ as $|\mathbf{r}| \to \infty$.

As a special case, setting $\epsilon_\infty = \epsilon_s$ reduces (18) to

$$-\epsilon_0\epsilon_s\Delta\left[W(\mathbf{r}) - \lambda^2\Delta W(\mathbf{r})\right] = \rho(\mathbf{r}), \quad \mathbf{r}\in\mathbb{R}^3, \tag{19}$$

where $W \to 0$ as $|\mathbf{r}| \to \infty$.

Furthermore, when $\lambda = 0$, the model (18) is reduced to the classic Poisson model:

$$-\epsilon_0\epsilon_s\Delta\Phi(\mathbf{r}) = \rho(\mathbf{r}) \quad \forall\mathbf{r}\in\mathbb{R}^3, \tag{20}$$

where $\Phi(\mathbf{r}) \to 0$ as $|\mathbf{r}| \to \infty$.

From the above description it can be seen that the solutions of (18) and (19) are the convolutions of the solutions of nonlocal Poisson dielectric model (11) and local Poisson dielectric model (20), respectively, with respect to the Yukawa-like kernel function Q_λ. For clarity, we will call (18) and (19) *a nonlocal Poisson-Fermi model* and *a local Poisson-Fermi model*, respectively.

Note that our local Poisson-Fermi model (19) is a significant generalization of Santangelo's fourth-order model [72] since in Santangelo's model, the solution is simply treated as an electrostatic potential function, which is usually quite different from W.

Clearly, with a sufficiently large domain Ω, we can approximate (18) as the boundary value problem:

$$\begin{cases} -\epsilon_0\epsilon_s\Delta\left[W(\mathbf{r}) - l_c^2\Delta W(\mathbf{r})\right] = \rho(\mathbf{r}), & \mathbf{r}\in\Omega, \\ W(\mathbf{s}) = 0, & \mathbf{s}\in\partial\Omega, \end{cases} \tag{21}$$

where $\partial\Omega$ denotes the boundary of Ω.

Similar to what was done in [86], we can show that the above boundary value problem has a unique solution, and there exists a continuous self-adjoint positive linear operator, L, such that the solution can be expressed in the operator form

$$W = L^{-1}\rho \quad \text{for } \rho\in L^2(\Omega), \tag{22}$$

where L^{-1} denotes the inverse of L, and L is defined by

$$(LW, v) = \epsilon_0\epsilon_s\Big[l_c^2\sum_{i,j=1}^{3}\int_\Omega \frac{\partial^2 W}{\partial x_i\partial x_j}\frac{\partial^2 v}{\partial x_i\partial x_j}d\mathbf{r} + \sum_{i=1}^{3}\int_\Omega \frac{\partial W}{\partial x_i}\frac{\partial v}{\partial x_i}d\mathbf{r}\Big] \quad \forall v\in H_0^2(\Omega),$$

for $W \in H_0^2(\Omega)$. Here, $H_0^2(\Omega) = \{v \in H^2(\Omega) \mid v(\mathbf{s}) = 0\ \forall\mathbf{s}\in\partial\Omega\}$ with $H^2(\Omega)$ being a Sobolv space of functions with second order weak derivatives [1], $(u, v) = \int_\Omega u(\mathbf{r})v(\mathbf{r})d\mathbf{r}$ is an inner product for the Hilbert space $L^2(\Omega)$, which is a set of functions satisfying $(v, v) < \infty$.

To simplify the numerical calculation, we set

$$\Psi = -\Delta W$$

as a new unknown function to reformulate (21) as a system of two partial differential equations as follows:

$$\begin{cases} -\epsilon_0\epsilon_s\left[l_c^2\Delta\Psi(\mathbf{r}) - \Psi(\mathbf{r})\right] = \rho(\mathbf{r}), & \mathbf{r}\in\Omega, \\ \Delta W(\mathbf{r}) + \Psi(\mathbf{r}) = 0, & \mathbf{r}\in\Omega, \\ \Psi(\mathbf{s}) = 0, \quad W(\mathbf{s}) = 0, & \mathbf{s}\in\partial\Omega. \end{cases} \tag{23}$$

Using (17) and the solution (Ψ, W) of (23), we then obtain the nonlocal electrostatic potential Φ by

$$\Phi(\mathbf{r}) = W(\mathbf{r}) + \lambda^2\Psi(\mathbf{r}), \quad \mathbf{r}\in\Omega. \tag{24}$$

To understand the physical meaning of Ψ, we can use the multiplication properties of convolution to get

$$\begin{aligned}\Psi(\mathbf{r}) &= -\Delta W(\mathbf{r}) = -\Delta(\Phi * Q_\lambda)(\mathbf{r}) = -(\Delta\Phi * Q_\lambda)(\mathbf{r}) \\ &= \frac{1}{\epsilon_0\epsilon_s}(\rho * Q_\lambda)(\mathbf{r}) + \frac{\epsilon_s - \epsilon_\infty}{\epsilon_\infty}(W * Q_\lambda)(\mathbf{r}).\end{aligned} \tag{25}$$

In the case of the local Poisson model (20) (i.e., $\epsilon_\infty = \epsilon_s$), the above expression is simplified as

$$\begin{aligned}\Psi(\mathbf{r}) &= -\Delta W(\mathbf{r}) = -\Delta(\Phi * Q_\lambda)(\mathbf{r}) \\ &= -(\Delta\Phi * Q_\lambda)(\mathbf{r}) = \frac{1}{\epsilon_0\epsilon_s}(\rho * Q_\lambda)(\mathbf{r}).\end{aligned}$$

Hence, when the charge density function ρ is estimated in terms of ionic concentration functions c_i for $i = 1, 2, \ldots, n$ for a solvent containing n different ionic species in the expression

$$\rho(\mathbf{r}) = e_c\sum_{i=1}^{n} Z_i c_i(\mathbf{r}), \quad \mathbf{r}\in\Omega, \tag{26}$$

where Z_i is the charge number of ionic species i, we can use (25) to find that

$$\Psi(\mathbf{r}) = \frac{e_c}{\epsilon_0\epsilon_s}\sum_{i=1}^{n} Z_i(c_i * Q_\lambda)(\mathbf{r}) + \frac{\epsilon_s - \epsilon_\infty}{\epsilon_\infty}(W * Q_\lambda)(\mathbf{r}).$$

This shows that Ψ can be used to reflect ionic size effects through properly selecting c_i. For this reason, the formula (24) becomes significantly important since it has split the electrostatic potential Φ into two component functions, Ψ and W, to reflect both the ionic size effects and permittivity correlations among water molecules.

IV. A NONLOCAL FERMI DISTRIBUTION

In this section, we derive a nonlocal Fermi distribution for an ionic solvent containing n different ionic species, and show that it leads to optimal ionic concentrations in the sense of minimizing an electrostatic free energy, which we construct as a modification of the traditional one commonly used in the PBE study.

Clearly, applying (26) to (22), we can express the solution W of the nonlocal Poisson-Fermi equation (21) as a function of ionic concentrations c_i for $i = 1, 2, \ldots, n$ in the operator form

$$W = e_c \sum_{i=1}^{n} Z_i L^{-1} c_i, \tag{27}$$

from which it implies that different ionic concentrations may result in different potential functions of W. Hence, it is interesting to search for a set of optimal ionic concentration functions to yield an optimal potential in the sense of an electrostatic free energy minimization. One key step to do so is to construct a proper electrostatic free energy functional in terms of ionic concentration functions.

To do so, we denote c_{n+1} as the concentration function of water molecules, and treat the ions and water molecules as the hard-spherical balls with radius a_i for $i = 1, 2, \ldots, n, n+1$. Thus, the volume of each ball is given by $4\pi a_i^3/3$. In the ion channel study done in [57], the interstitial voids among these balls were considered in the calculation of ionic concentration functions. Similarly, to reflect the size effects of these voids, we define two void volume fraction functions, Γ^b and $\Gamma(\mathbf{r})$, respectively, by the two size constrain conditions

$$\frac{4\pi}{3}\sum_{i=1}^{n+1} a_i^3 c_i^b + \Gamma^b = 1, \quad \frac{4\pi}{3}\sum_{i=1}^{n+1} a_i^3 c_i(\mathbf{r}) + \Gamma(\mathbf{r}) = 1, \tag{28}$$

where c_i^b denotes the bath concentration of the ith species for $i = 1$ to $n+1$. We then follow what was done in the derivation of Boltzmann distribution from the PBE study [48, 49, 86], to select c_i for $i = 1, 2, \ldots, n+1$ optimally as a solution of the following electrostatic free energy minimization problem

$$\min\{F(c) | c = (c_1, c_2, \ldots, c_n, c_{n+1}) \text{ with } c_i \in C(\Omega)\}, \tag{29}$$

where $F(c) = F_{es}(c) + F_{id}(c) + F_{ex}(c)$ with F_{es}, F_{id}, and F_{ex} being the electrostatic, ideal gas, and excess energies, respectively, as defined by

$$F_{es}(c) = \frac{e_c}{2}\sum_{i=1}^{n}\int_\Omega Z_i W(\mathbf{r}) c_i(\mathbf{r}) d\mathbf{r},$$

$$F_{id}(c) = k_B T \sum_{i=1}^{n+1}\int_\Omega c_i(\mathbf{r})\left[\ln\left(\frac{c_i}{c_i^b}\right) - 1\right] d\mathbf{r},$$

and

$$F_{ex}(c) = k_B T \int_\Omega \Gamma(\mathbf{r})\left[\ln\left(\frac{\Gamma(\mathbf{r})}{\Gamma^b}\right) - 1\right] d\mathbf{r}.$$

Here, Γ^b and Γ must be positive, and the excess energy is induced from the size constrain conditions of (28).

Theorem 1. *The minimization problem (29) has a unique solution. Moreover, the solution can be expressed in the Fermi distribution form*

$$c_i(\mathbf{r}) = c_i^b e^{-\left[\frac{e_c Z_i}{k_B T} W(\mathbf{r}) - \frac{4\pi a_i^3}{3} S^{trc}(\mathbf{r})\right]}, \tag{30}$$

where $i = 1, 2, \ldots, n+1$, Γ and Γ^b are defined in (28), W is a solution of the nonlocal Poisson-Fermi model (21), and S^{trc} is defined by

$$S^{trc}(\mathbf{r}) = \ln\left(\frac{\Gamma(\mathbf{r})}{\Gamma^b}\right).$$

Proof. Clearly, by (27), the electrostatic free energy F_{es} can be reformulated as

$$F_{es}(c) = \frac{e_c^2}{2}\sum_{i,j=1}^{n} Z_i Z_j \int_\Omega L^{-1} c_i c_j d\mathbf{r}.$$

We then can find the first and second Fréchet partial derivatives of F_{id}, F_{es}, and F_{ex} as follows:

$$\frac{\partial F_{id}(c)}{\partial c_i} = k_B T \ln\left(\frac{c_i}{c_i^b}\right),$$

$$\frac{\partial^2 F_{id}(c)}{\partial c_j \partial c_i} = \begin{cases} \frac{k_B T}{c_i} & j = i, \\ 0 & j \neq i, \end{cases}$$

$$\frac{\partial F_{es}(c)}{\partial c_i} = e_c Z_i W, \qquad \frac{\partial^2 F_{es}(c)}{\partial c_j \partial c_i} = e_c^2 Z_i Z_j L^{-1},$$

$$\frac{\partial F_{ex}(c)}{\partial c_i} = -k_B T \frac{4\pi a_i^3}{3} \ln\left(\frac{\Gamma(\mathbf{r})}{\Gamma^b}\right),$$

$$\frac{\partial^2 F_{ex}(c)}{\partial c_j \partial c_i} = k_B T \left(\frac{4\pi}{3}\right)^2 \frac{(a_i a_j)^3}{\Gamma(\mathbf{r})}.$$

Combining the above partial derivatives together, we get the first Fréchet derivative F' in the expression

$$F'(c)v = \sum_{i=1}^{n}\int_{D_s}\left[e_c Z_i W + k_B T \ln\left(\frac{c_i}{c_i^b}\right) - k_B T \frac{4\pi a_i^3}{3} \ln\left(\frac{\Gamma(\mathbf{r})}{\Gamma^b}\right)\right] v_i(\mathbf{r}) d\mathbf{r}.$$

From the stationary equation $F'(c)v = 0$ it implies the system of equations: For $i = 1, 2, \ldots, n+1$,

$$e_c Z_i W + k_B T \ln\left(\frac{c_i}{c_i^b}\right) - k_B T \frac{4\pi a_i^3}{3} \ln\left(\frac{\Gamma(\mathbf{r})}{\Gamma^b}\right) = 0. \tag{31}$$

Furthermore, we can obtain that the second Fréchet derivative F'' as below:

$$F''(c)(v, v) = e_c^2 \langle L^{-1}\sum_{i=1}^{n} Z_i v_i, \sum_{i=1}^{n} Z_i v_i\rangle_{L^2(\Omega)} + k_B T \sum_{i=1}^{n}\int_{D_s}\frac{1}{c_i}(v_i(\mathbf{r}))^2 d\mathbf{r} + \int_{D_s}\frac{k_B T}{\Gamma(\mathbf{r})}\left(\frac{4\pi}{3}\sum_{i=1}^{n} a_i^3 v_i\right)^2 d\mathbf{r}.$$

From the above expression it can imply that $F''(c)$ is strictly positive. Hence, the the minimization problem (29) has a unique solution. From (31) we can obtain the expressions of (30). This completes the proof.

The term S^{trc} is often referred to as *a steric potential* since it describes ionic size effects caused by the ionic size constraint conditions (28) [57]. This is the reason why the expression of (30) can be called *a Fermi distribution*.

Specially, when all the radii $a_i = 0$, the Fermi distribution is reduced to the Boltzmann distribution

$$c_i(\mathbf{r}) = c_i^b e^{-Z_i \frac{e_c}{k_B T} W(\mathbf{r})}, \quad i = 1, 2, \ldots, n.$$

In addition, setting the correlation length parameter $\lambda = 0$ (without considering any dielectric correlation effect), we obtain the classic Boltzmann distribution

$$c_i(\mathbf{r}) = c_i^b e^{-Z_i \frac{e_c}{k_B T} \Phi(\mathbf{r})}, \quad i = 1, 2, \ldots, n,$$

where Φ is the solution of the local Poisson dielectric equation (20).

V. A DIMENSIONLESS NONLOCAL POISSON-FERMI MODEL

A combination of (31) and (26) with (21) immediately results in a system of $n+2$ equations for solving the electrostatic potential W and concentration functions $\{c_i\}$ as follows:

$$\begin{cases} -\epsilon_0 \epsilon_s \Delta \left[W - l_c^2 \Delta W \right] = e_c \sum_{i=1}^{n} Z_i c_i(\mathbf{r}), \ \mathbf{r} \in \Omega, \\ Z_i \frac{e_c}{k_B T} W + \ln\left(\frac{c_i}{c_i^b}\right) - \frac{4\pi}{3} a_i^3 \ln\left(\frac{\Gamma(\mathbf{r})}{\Gamma^b}\right) = 0, \\ \qquad \mathbf{r} \in \Omega \quad \text{for } i = 1, 2, \ldots, n+1, \\ W(\mathbf{s}) = 0, \quad \Delta W(\mathbf{s}) = 0, \quad \mathbf{s} \in \partial\Omega. \end{cases} \tag{32}$$

In biomolecular simulation, length is measured in angstroms (Å), and c_i is in moles per liter. Thus, we need to convert c_i to the number concentration (i.e., the number of ions per cubic angstroms) by

$$c_i \text{ moles per liter} = c_i N_A 10^{-27} / \text{Å}^3.$$

We then reformulate both $\Gamma(\mathbf{r})$ and Γ^b as follows:

$$\Gamma(\mathbf{r}) = 1 - \tfrac{4\pi N_A}{3\times 10^{27}} \sum_{i=1}^{n+1} a_i^3 c_i(\mathbf{r}), \tag{33a}$$

$$\Gamma^b = 1 - \tfrac{4\pi N_A}{3\times 10^{27}} \sum_{i=1}^{n+1} a_i^3 c_i^b. \tag{33b}$$

Furthermore, by the variable changes

$$u = \frac{e_c}{k_B T} W, \qquad \text{and} \quad \Psi = -\Delta u,$$

the nonlocal Poisson-Fermi model (32) is reformulated into the dimensionless form

$$\begin{cases} -\epsilon_s l_c^2 \Delta \Psi + \epsilon_s \Psi = \frac{e_c^2 N_A}{\epsilon_0 k_B T 10^{27}} \sum_{i=1}^{n} Z_i c_i \quad \text{in } \Omega, \\ \Delta u + \Psi = 0 \quad \text{in } \Omega, \\ Z_i u + \ln(c_i) - \frac{4\pi}{3} a_i^3 \ln \Gamma(\mathbf{r}) = \ln(c_i^b) \\ \quad - \frac{4\pi}{3} a_i^3 \ln(\Gamma^b) \text{ in } \Omega \text{ for } i = 1, 2, \ldots, n+1, \\ u(\mathbf{s}) = 0, \quad \Psi(\mathbf{s}) = 0, \quad \mathbf{s} \in \partial\Omega, \end{cases} \tag{34}$$

where $\Gamma(\mathbf{r})$ and Γ^b are given in (33).

To ensure the definition of the above system, both $\Gamma(\mathbf{r})$ and Γ^b are required to be positive almost every where. In the following theorem, we present a sufficient condition to satisfy such a requirement.

Theorem 2. *Let $\Gamma(\mathbf{r})$ and Γ^b be defined in (33). If all the concentration functions c_j satisfy the range constraints*

$$0 < c_j(\mathbf{r}) < \frac{3 \times 10^{27}}{4\pi N_A \sum_{i=1}^{n+1} a_i^3}, \quad j = 1, 2, \ldots, n+1, \tag{35}$$

then both $\Gamma(\mathbf{r})$ and Γ^b are positive. Moreover, if $0 < c_i^b \le M_1$ for $i = 1, 2, \ldots, n$, and $0 < c_{n+1}^b \le M_2$, then a lower bound of Γ^b is given by

$$\Gamma^b \ge 1 - \frac{4\pi N_A}{3 \times 10^{27}} \left[M_1 \sum_{i=1}^{n} a_i^3 + a_{n+1}^3 M_2 \right], \tag{36}$$

where M_1 and M_2 are two given upper bounds such that the above lower bound is positive.

Proof. By the inequality

$$c_i(\mathbf{r}) \le \max_{1 \le j \le n+1} \max_{\mathbf{r} \in \Omega} c_j(\mathbf{r}),$$

we can get

$$\Gamma(\mathbf{r}) > 1 - \frac{4\pi N_A}{3 \times 10^{27}} \sum_{i=1}^{n+1} a_i^3 \max_{1 \le j \le n+1} \max_{\mathbf{r} \in \Omega} c_j(\mathbf{r})$$

for $\mathbf{r} \in \Omega$ except a measure zero set.

Thus, $\Gamma(\mathbf{r}) > 0$ provided that

$$1 - \frac{4\pi N_A}{3 \times 10^{27}} \sum_{i=1}^{n+1} a_i^3 \max_{1 \le j \le n+1} \max_{\mathbf{r} \in \Omega} c_j(\mathbf{r}) > 0,$$

from which it implies the sufficient condition (35). The proof of (36) is trivial. This completes the proof.

VI. NUMERICAL STABILITY PROBLEM

However, the range constraint condition (35) may cause a numerical stability problem in the calculation of concentration functions. To illustrate this issue, we first construct two numerical algorithms, called Algorithms 1

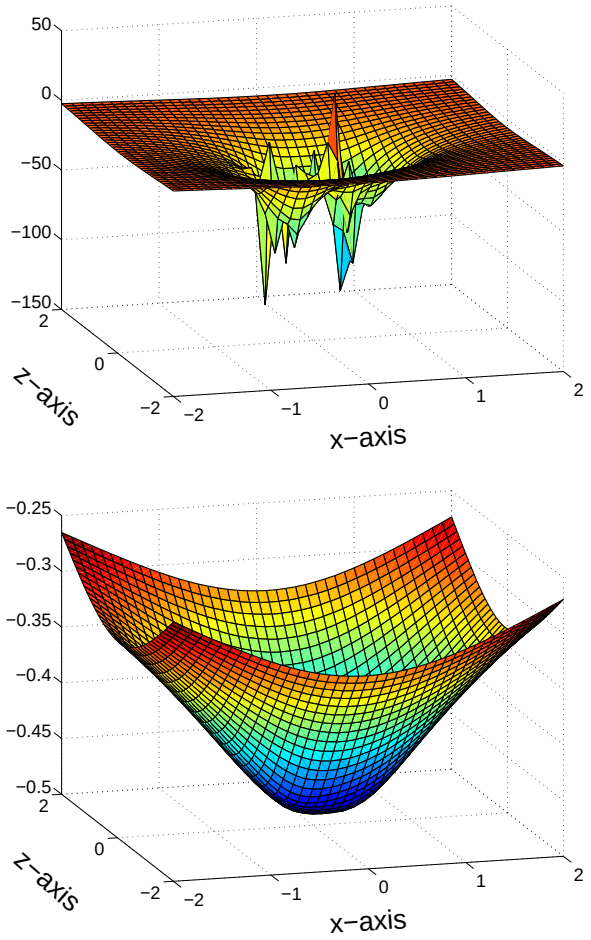

FIG. 2: A comparison of the solution Φ of a nonlocal Poisson dielectric test model with the solution W of the corresponding nonlocal Poisson-Fermi model (in a view with $y = 0$) for a dielectric unit ball containing 488 point charges from a protein (PDB ID: 2LZX). Here, $W = \Phi * Q_\lambda$, and the series expressions of Φ and W given in [88] were used to plot the top figure for Φ and the bottom figure for W.

and 2. We then use them to show that the Poisson-Fermi approach is very likely to improve the numerical stability of the classic Poisson dielectric approach in the calculation of ionic concentrations.

To construct a simple iterative scheme for computing concentration functions, we treat the nonlinear system (34) as a differential-algebraic equation problem. That is, the boundary value problem

$$\begin{cases} -\epsilon_s l_c^2 \Delta\Psi + \epsilon_s \Psi = \frac{e_c^2 N_A}{\epsilon_0 k_B T 10^{27}} \sum_{i=1}^{n} Z_i c_i, & \mathbf{r} \in \Omega, \\ \Delta u + \Psi = 0, & \mathbf{r} \in \Omega, \\ u(\mathbf{s}) = 0, \quad \Psi(\mathbf{s}) = 0, & \mathbf{s} \in \partial\Omega, \end{cases}$$

subject to the following system of $n+1$ nonlinear algebraic equations: For $i = 1, 2, \ldots, n+1$,

$$Z_i u + \ln(c_i) - \frac{4\pi}{3} a_i^3 \ln \Gamma(\mathbf{r}) = \ln(c_i^b) - \frac{4\pi}{3} a_i^3 \ln(\Gamma^b).$$

We then reformulate the above algebraic equations as

$$c_i(\mathbf{r}) = \frac{c_i^b e^{-Z_i u(\mathbf{r})}}{(\Gamma^b)^{4\pi a_i^3/3}} \left(1 - \frac{4\pi N_A}{3 \times 10^{27}} \sum_{i=1}^{n+1} a_i^3 c_i(\mathbf{r})\right)^{\frac{4\pi a_i^3}{3}},$$

from which we construct a simple iterative scheme for computing concentration functions c_i in Algorithm 1.

Algorithm 1. *Let $c_i^{(k)}$ denote the k-th iterative approximation to the concentration function c_i for $i = 1, 2, \ldots, n+1$. The following four steps are carried out for $k = 0, 1, 2, \ldots$ until a convergence rule is satisfied:*

Step 1.: *Set an initial guess, $c_i^{(0)}$, and $k = 0$.*

Step 2.: *Calculate the k-th iterate $u^{(k)}$ by solving the nonlocal Poisson-Fermi boundary value problem*

$$\begin{cases} -\epsilon_s l_c^2 \Delta\Psi + \epsilon_s \Psi = \frac{e_c^2 N_A}{\epsilon_0 k_B T 10^{27}} \sum_{i=1}^{n} Z_i c_i^{(k)}, & \mathbf{r} \in \Omega, \\ \Delta u + \Psi = 0, & \mathbf{r} \in \Omega, \\ u(\mathbf{s}) = 0, \quad \Psi(\mathbf{s}) = 0, & \mathbf{s} \in \partial\Omega, \end{cases}$$

Step 3.: *Define the update $c_i^{(k+1)}$ for $i = 1, 2, \ldots, n+1$ by the recursive formula*

$$c_i^{(k+1)}(\mathbf{r}) = \frac{c_i^b e^{-Z_i u^{(k)}(\mathbf{r})}}{(\Gamma^b)^{4\pi a_i^3/3}} \left(1 - \frac{4\pi N_A}{3 \times 10^{27}} \sum_{i=1}^{n+1} a_i^3 c_i^{(k)}(\mathbf{r})\right)^{\frac{4\pi a_i^3}{3}}.$$

Step 4.: *Check the convergence:*
If $\|c_i^{(k+1)} - c_i^{(k)}\| < \eta$ (e.g., $\eta = 10^{-5}$), stop the iteration; otherwise, increase k by one, and go back to Step 2.

Algorithm 2 can be constructed as a modification of Algorithm 1 by substituting $u^{(k)}$ as $\hat{u}^{(k)}$ with

$$\hat{u}^{(k)} = e_c \Phi^{(k)} / (k_B T),$$

where $\Phi^{(k)}$ denotes a solution of the nonlocal Poisson dielectric model (11) using the boundary condition $\Phi = 0$ on $\partial\Omega$ and the charge density $\rho(\mathbf{r}) = e_c \sum_{i=1}^{n} Z_i c_i^{(k)}(\mathbf{r})$.

We next use Algorithms 1 and 2 to illustrate why a Poisson-Fermi model is more favorable than the corresponding Poisson model in the calculation of ionic concentrations. To do so, we only need to show that $u^{(k)}$ has a smaller range than $\hat{u}^{(k)}$ due to the fact that the value scale of the update $c_i^{(k+1)}$ is mainly determined by the factor $e^{-Z_i u^{(k)}}$ in Algorithm 1 or $e^{-Z_i \hat{u}^{(k)}}$ in Algorithms 2. We further observe that $u^{(k)}$ is the convolution

of $\hat{u}^{(k)}$ with respect to the Yukawa-like kernel Q_λ; thus, $u^{(k)}$ can have a much smaller range than $\hat{u}^{(k)}$ since the convolution can sharply reduce the range of a potential function in general. Therefore, Algorithm 1 is expected to be more stable numerically than Algorithm.

As an example, we estimated the upper bound of the constraint condition (35) for the NaCl electrolyte. In this numerical test, we had $n = 2$, $Z_1 = 1, Z_2 = -1$, and $c_1^b = c_2^b = I_s$. We then set $a_1 = 0.95, a_2 = 1.81$, and $a_3 = 1.4$ as the radii of Na^+, Cl^-, and water molecule H_2O, respectively [58]. In this case, we got

$$0 < c_i(\mathbf{r}) < 41.6, \quad \mathbf{r} \in \Omega \quad \text{for } i = 1, 2, 3,$$

confirming that the range of each ionic concentration that ensures $\Gamma(\mathbf{r}) > 0$ can be small. Using (36), we also got

$$\Gamma^b > 0.56 \quad \text{when } I_s < 2.5 \text{ and } c_3^b < 55.$$

We next calculated the solution Φ of a simple nonlocal Poisson test model (called Model 1 in Xie *et al*'s recent work [88]) and its convolution $W = \Phi * Q_\lambda$ as an example for demonstrating that the convolution can sharply reduce the range of Φ.

In this test, we set the solvent region $\Omega = (-2, -2)^3 \setminus D_p$ with $D_p = \{\mathbf{r} \mid |\mathbf{r}| < 1\}$, $\epsilon_p = 2$, $\epsilon_s = 80$, $\epsilon_\infty = 1.8$, and $\lambda = 10$. A set of 488 atomic charges from a protein with 488 atoms (PDB ID: 2LXZ) were scaled to the unit ball D_p such that each charge position has a length less than 0.8. The series expressions of Φ and W were given in [88]. Using them, we calculated Φ and W approximately as a partial sum of the series with 20 terms, which was found to have a relative error $O(10^{-5})$ with respect to the partial sum calculated by 100 terms. Here we used the physical parameter values of ϵ_0, e_c, T, and k_B given in [82, Table 1].

Figure 2 shows that the Poisson-Fermi solution W is much smoother than the Poisson solution Φ, implying that the Poisson-Fermi model can be much easier to solve numerically to high accuracy than the corresponding Poisson dielectric model.

The ranges of W and Φ within the solvent region Ω were found to be $[-0.4363, -0.2273]$ and $[-37.7190, -1.2484]$, respectively, confirming that the convolution has a much smaller range than the corresponding potential function. Consequently, Algorithm 1 can be more numerically stable than Algorithm 2 under the constrain condition (35).

VII. CONCLUSIONS

Ions always interact in water solutions, because ions are charged and so is water (although the net charge of a water molecule is zero). The interactions of ions and water and the interactions of ions with each other have been studied extensively, first treating ions as points. Recently, the finite size of ions has been dealt with successfully in models that are easy to compute, both in flow and in mixtures, with a Fermi distribution coupled to a Poisson equation using the Santangelo equation to link electric field near and far from ions. The Fermi distribution describes the main difference between points and finite size ions. Finite size ions cannot overfill space. Points can fill space to any density including 'infinity'.

In this work, we generalize the Santangelo equation using Xie *et al*'s nonlocal Poisson dielectric theory, and find a generalization that is a convolution of previous results with a Yukawa like potential. Our new formula for estimating the nonlocal parameter λ depends on and varies with ionic strength of various types of ions (mixtures in solvent). This is very different from Santagelo's model in which the parameter is a correlation length that is not specifically related to ionic strength and hence does not change with varying bulk concentrations of all ionic species. Our nonlocal Fermi distribution is new due to the specific ionic radius associated with the steric potential. It has been shown to be optimal in the sense of minimizing an electrostatic free energy, which we construct using the bulk concentrations and ionic size constraint conditions. We combine our general Poisson-Fermi model with this new Fermi distribution to create a nonlocal Poisson Fermi theory for computing both the convolution of electrostatic potential and ionic concentrations. Furthermore, ionic concentrations are found to have limited ranges to ensure the definition of a Poisson-Fermi model. The convolution smooths and so results are even easier to compute than in the local theory. It also reduces the range of a corresponding potential function sharply. Hence, a Poisson-Fermi model is particularly valuable in the development of effective numerical algorithms for computing ionic concentrations.

Later work will examine how well the nonlocal Poisson Fermi model fits experimental data. Moreover, this new model will be adapted to the study of biomolecules (e.g., nucleic acids and proteins) and biological applications that involve ionic flows and concentrated ionic mixtures. Indeed, the flows, ionic mixtures, or (average global) concentrations occur in all biological and almost all technological applications. Ions tend to be concentrated where they are important and Liu and Eisenberg's Poisson-Nernst-Planck-Fermi (PNPF) model has done surprisingly well in dealing with them. As an application of our new nonlocal Fermi theory, we will develop a nonlocal PNPF model for ion channel in the future.

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