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-like kernel function. The Fermi distribution is shown to be a set of optimal ionic concentration functions in the sense of minimizing an electrostatic potential free energy. 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 with the Poisson-Boltzmann equation (PBE) as a starting point. The PBE model has its successes [1–11], particularly compared to the treatment of ionic solutions by the theory of ideal (uncharged) perfect gases, found in biochemistry texts [12,13]. But the successes of PBE are mostly qualitative because PBE distinguishes between ions only by charge. PBE does not distinguish between sodium and potassium ions, for example. Real ionic solutions have nonideal excess properties 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 [9,13–29]. As Nobelist Aaron Klug (over-) states the issue [30]: "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 50 years, says "... many workers adopt a counsel of despair, confining their interest to concentrations below about 0.02 M..." [31, p. 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 0.1 M or so" [23, p. 10]. These issues are discussed, and some of the innumerable corroborating references are listed in [14,15,17–19,21–26,28,29,31–40]. 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 charged solvent water. Water is a complex distribution of charge, more or less a dipole plus a quadrupole, with zero net charge but large local charges arising from the asymmetrical charge distribution in the chemical bonds between oxygen and hydrogen atoms. 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 [41–43])—have nonideal properties mostly because they are spheres not points. 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 [44]. Where they are most important, ion concentrations are usually more than 10 molar, often reaching 100 molar (!), more concentrated than Na^+Cl^- in table salt (37 molar). This surprising fact is the subject of the reviews [19,34,35], 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 [44] and in Rb^+ binding sites in the KcsA potassium channel [27].

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 [19,34,35,45,46] and ion channels, starting with approximate treatments of bulk solutions, moving to Monte Carlo simulations of all sphere systems, culminating in a variational treatment [16] that combines diffusion,

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migration, and convection using the energetic variational approach pioneered by Chun Liu [47,48] more than anyone else.

The variational treatment, however, computes forces (that can become very large) 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 approach derived by J. Liu and Eisenberg in the calculation of the entropy of an arbitrary mixture of spheres of any diameter in various systems [45,46,49–52]. 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 [53] that has been popularized by [54] and others [55].

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 type and concentration. 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 is needed, which is more general and nonlocal, and that is what we provide here.

The study of nonlocal dielectric continuum models was started 30 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 [56–63]. Because of the complexity and difficulty of 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 [64–67]. 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) [68], opening a way to solve a nonlocal model numerically by advanced PDE numerical techniques [69,70]. Motivated by Hildebrandt *et al.*'s work, Xie *et al.* adopted different techniques from those 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 [71]. Their reformulation techniques were then applied to the construction of a new nonlocal dielectric model for protein in water [72] and a general nonlocal Poisson dielectric model for proteins in ionic solvents [73,74]. 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 has recently been derived as a nonlinear and nonlocal dielectric continuum model for protein in ionic solvent [73].

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, which includes Santangelo's fourth-order partial differential equation (PDE) model and the classic Poisson dielectric model as two special cases. In our new nonlocal treatment, Santangelo's model is equivalent to a convolution of the classic Poisson dielectric model with a Yukawa-like kernel function.

Interestingly, we observe that an electrostatic potential function can be split into two functions—one for nonlocal dielectric effects and the other for ionic size effects for an ionic solvent as a mixture of spheres with different radii. We also note that these two functions can be found from solving the Poisson-Fermi model when the model is reformulated from a fourth-order PDE boundary value problem into a system of two coupled second-order PDEs. Clearly, as a fourth-order PBE model, a Poisson-Fermi equation can have a much smoother solution than a Poisson model. Hence, it is expected to be much easier to solve numerically. This is one reason why a Poisson-Fermi model deserves to be studied in dielectric continuum modeling.

One significant feature of the Fermi-like distribution derived by Liu and Eisenberg (see [52, Eq. (10)]) is its treatment of interstitial voids as an additional particle species. However, since the size of each void is position dependent, it is difficult to define a concentration of the voids. We avoid this difficulty in this paper by constructing a new electrostatic free energy functional. In fact, as a modification of the traditional electrostatic free energy functional commonly used in the PBE study (see [75,76], for example), our new electrostatic free energy functional has an excess energy term that reflects the properties of the the interstitial voids and of ion size. The new functional involves only the bulk concentrations of ions and water molecules and the radii of ions and water molecules. In contrast, the traditional electrostatic free energy functional requires a chemical potential constant for each ionic species, which may be difficult to obtain and in fact varies from one experimental condition to another. By minimizing our new electrostatic free energy functional, a new nonlocal Fermi distribution is produced for defining optimal concentration functions for ionic species and water molecules. Consequently, we obtain the new nonlocal Poisson-Fermi model for computing the electrostatic potential, its convolution, and the concentrations of ionic species and water molecules.

The Poisson-Fermi model is highly nonlinear because the state energy of any particle in the generalized Boltzmann (Fermi) distribution function contains both electric and steric potentials. In addition to the self-consistent issue associated with the electric potential in solving the Poisson equation as usual, the solution process must also be self-consistent with

the steric potential. In other words, the Poisson equation for the electric potential, the steric potential of nonuniform size effects, and the $n+1$ nonlinear algebraic equations for the concentration functions of n ionic species and water molecules are all strongly coupled together. Numerical stability is of great concern when solving the Poisson-Fermi model by an iterative method.

As an initial study of the issue of numerical stability, we obtain boundedness conditions that can ensure the numerical stability of an iterative search algorithm (such as Newton's method) for computing concentration functions and an electrostatic potential function when the size effects of ions and water are taken into account. We then made numerical tests to illustrate the reason why our Poisson-Fermi model can be more stable numerically than the corresponding Poisson dielectric model.

We organize the remaining part of the paper as follows. In Sec. II, we review the nonlocal Poisson dielectric model, and obtain the new formula for estimating an important nonlocal model parameter. In Sec. III, we present the new nonlocal Poisson-Fermi model, and show that its solution is a convolution of the solution of a nonlocal Poisson dielectric model. In Sec. IV, we derive the new nonlocal Fermi distribution as a minimization of our new electrostatic free energy functional. In Sec. V, we reformulate the Poisson-Fermi model in a dimensionless form, and obtain sufficient conditions to guarantee its definition. In Sec. VI, we discuss a numerical stability issue and report related numerical results. Finally, the conclusions are made in Sec. 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:

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

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 [77,78] has been established based on the linear relationships of displacement field $\mathbf{d}$ and polarization field $\mathbf{p}$ with $\mathbf{e}$:

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

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

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

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

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

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

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

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

It has been known that the relationship (2) depends on a spatial frequency of a dielectric medium (see [79] for example). To reflect this feature, the spatial frequency variable of the Fourier transform is used to describe the spatial dependence of the dielectric so that the two linear relationships of (2) are mimicked in the Fourier frequency space as follows:

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

where $\widehat{\varepsilon}(\mathbf{k}), \widehat{\chi}(\mathbf{k}), \widehat{\mathbf{d}}(\mathbf{k}), \widehat{\mathbf{p}}(\mathbf{k})$, and $\widehat{\mathbf{e}}(\mathbf{k})$ 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 [56]. Applying the inverse Fourier transform to (6), we obtain the nonlocal relationships of $\mathbf{d}$ and $\mathbf{p}$ with $\mathbf{e}$:

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

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

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

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

where $\Phi(\mathbf{r}) \to 0$ as $|\mathbf{r}| \to \infty$. In particular, following Debye's (temporal) frequency-dependent permittivity function (see [56, p. 100] and [79], for example), we set $\widehat{\varepsilon}$ in the expression,

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

where ε_s and ε_∞ are the static and optic values corresponding to the spatial frequencies $|\mathbf{k}| = 0$ and $|\mathbf{k}| \to \infty$, 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) [81,82]. 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 [83], 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 $\mathbf{r} \in \mathbb{R}^3$,

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

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

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

Furthermore, by the derivative properties of the convolution [83, Theorem 6.30, p. 171], we can detach the derivatives from the integral term to get

$$(\nabla\Phi * Q_\lambda)(\mathbf{r}) = \nabla(\Phi * Q_\lambda)(\mathbf{r}).$$

The nonlocal Poisson dielectric model (11) can then be reformulated in the form,

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

where $\Delta=\sum_{i=1}^{3}\frac{\partial^2}{\partial x_i^2}$ is the Laplace operator.

One interesting issue in the study of the nonlocal Poisson dielectric model comes from the selection of parameter λ. Many studies have been performed with different ionic solvents in a range of applications [20,21,32,40,84], [71, Fig. 2.1], and [69,81], showing that a value of λ can vary from 3 to 25.

While a value of λ can be determined from experiments, for an ionic solution, 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 [80], which satisfies the distribution equation,

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

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

$$-\epsilon_s\Delta u(\mathbf{r})+\kappa^2u(\mathbf{r})=\frac{10^{10}e_c^2}{\epsilon_0k_BT}z\delta(\mathbf{r}),\quad \mathbf{r}\in\mathbb{R}^3,\quad (14)$$

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

$$\kappa=\frac{e_c}{10^8\sqrt{5}}\left(\frac{N_AI_s}{\epsilon_0k_BT}\right)^{1/2},\quad (15)$$

with N_A being the Avogadro number ($N_A=6.02214129\times10^{23}$) and I_s the ionic solvent strength. Clearly, the Debye-Hückel equation is reduced to (13) in the case that $z=\epsilon_0\epsilon_sk_BT/(10^{10}e_c^2)$, and $\lambda=\sqrt{\epsilon_s}/\kappa$, from which we obtain a formula for estimating λ:

$$\lambda=\frac{10^8\sqrt{5}}{e_c}\left(\frac{\epsilon_0\epsilon_sk_BT}{N_AI_s}\right)^{1/2}.\quad (16)$$

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 [85, Table 1], λ was found to have the range $4.3\leqslant\lambda\leqslant30.7$ for $0.01\leqslant I_s\leqslant0.5$ as displayed in Fig. 1. Further studies will be done on a proper selection of λ.

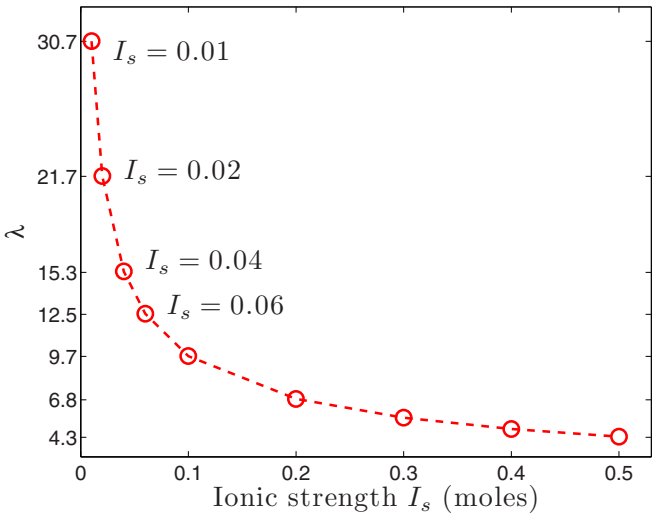

FIG. 1. The correlation length parameter λ predicted by formula (16) as a decreasing function of I_s.

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

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

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.

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:

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

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:

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

where $W\to0$ and $\Delta W\to0$ as $|\mathbf{r}|\to\infty$, which are followed from (17) and $\Phi\to0$ as $|\mathbf{r}|\to\infty$.

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

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

where $W\to0$ as $|\mathbf{r}|\to\infty$.

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

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

where $\Phi(\mathbf{r})\to0$ 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 the nonlocal Poisson dielectric model (11) and the local Poisson dielectric model (20), respectively, with respect to the Yukawa-like kernel function Q_λ. For clarity, we will call (18) *a nonlocal Poisson-Fermi model*.

In general, the convolution $\Phi*Q_\lambda$ can be much smoother than Φ without involving any singularity over the whole space $\mathbb{R}^3$ (see Fig. 2, for example). Hence, a Poisson-Fermi model

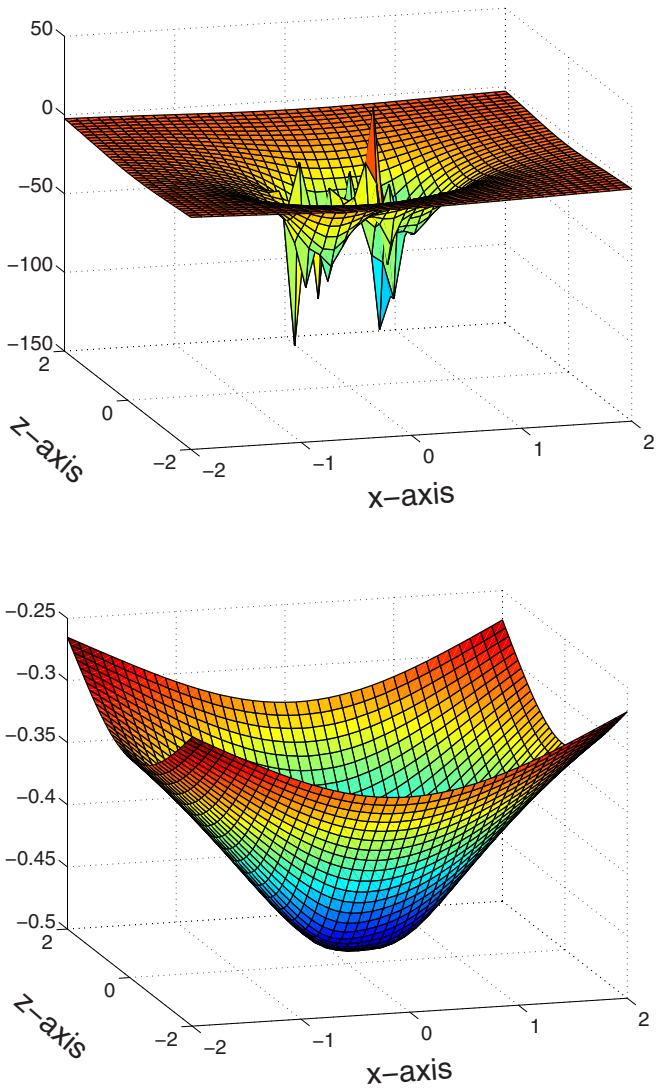

FIG. 2. A comparison of a nonlocal Poisson model solution Φ (top plot) with a nonlocal Poisson-Fermi model solution W of Φ (bottom plot) in a view using $\mathbf{r} = (x,0,z)$ for a test model with a dielectric unit ball containing 488 charges from a protein (PDB ID: 2LZX).

can be much easier to solve numerically and should give a much more accurate numerical solution than the corresponding Poisson model.

Note that our local Poisson-Fermi model (19) is a significant generalization of Santangelo's fourth-order model [53] 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 bounded domain Ω of $\mathbb{R}^3$, we can approximate (18) as a boundary value problem as follows:

$$\begin{aligned} -\epsilon_0\epsilon_s\Delta\big[W(\mathbf{r}) - l_c^2\Delta W(\mathbf{r})\big] &= \rho(\mathbf{r}), \quad \mathbf{r}\in\Omega, \\ W(\mathbf{s}) = g_1(s), \quad \Delta W(\mathbf{s}) &= g_2(\mathbf{s}), \quad \mathbf{s}\in\partial\Omega, \end{aligned} \tag{21}$$

where g_1 and g_2 are two boundary value functions, and $\partial\Omega$ denotes the boundary of Ω. For example, we can simply set $g_1 = 0$ and $g_2 = 0$ when Ω is large enough.

To simplify the numerical solution of the above fourth-order PDE boundary value problem, we set

$$\Psi = -\Delta W$$

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

$$\begin{aligned} -\epsilon_0\epsilon_s\big[l_c^2\Delta\Psi(\mathbf{r}) - \Psi(\mathbf{r})\big] &= \rho(\mathbf{r}), \quad \mathbf{r}\in\Omega, \\ \Delta W(\mathbf{r}) + \Psi(\mathbf{r}) &= 0, \quad \mathbf{r}\in\Omega, \\ W(\mathbf{s}) = g_1(s), \quad \Psi(\mathbf{s}) &= -g_2(s), \quad \mathbf{s}\in\partial\Omega. \end{aligned} \tag{22}$$

Using (17) and the solution (Ψ, W) of (22), we then obtain the nonlocal electrostatic potential Φ by

$$\Phi(\mathbf{r}) = W(\mathbf{r}) + \lambda^2\Psi(\mathbf{r}), \quad \mathbf{r}\in\Omega. \tag{23}$$

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

$$\begin{aligned} \Psi(\mathbf{r}) &= -\Delta W(\mathbf{r}) = -\Delta(\Phi * Q_\lambda)(\mathbf{r}) = -(\Delta\Phi * Q_\lambda)(\mathbf{r}) \\ &= \frac{1}{\epsilon_0\epsilon_s}(\rho * Q_\lambda)(\mathbf{r}) + \frac{\epsilon_s - \epsilon_\infty}{\epsilon_\infty}(W * Q_\lambda)(\mathbf{r}). \end{aligned} \tag{24}$$

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

$$\rho(\mathbf{r}) = e_c\sum_{i=1}^{n} Z_i c_i(\mathbf{r}), \quad \mathbf{r}\in\Omega, \tag{25}$$

where Z_i is the charge number of ionic species i, we can use (24) 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 by the choice of c_i. Substituting the above expression into (23), we obtain a solution splitting formula for the nonlocal Poisson model (11) in the form,

$$\Phi(\mathbf{r}) = \Phi_w(\mathbf{r}) + \Phi_c(\mathbf{r}), \quad \mathbf{r}\in\Omega, \tag{26}$$

where Φ_w and Φ_c are defined by

$$\Phi_w(\mathbf{r}) = W(\mathbf{r}) + \frac{\lambda^2(\epsilon_s - \epsilon_\infty)}{\epsilon_\infty}(W * Q_\lambda)(\mathbf{r}),$$

and

$$\Phi_c(\mathbf{r}) = \frac{e_c\lambda^2}{\epsilon_0\epsilon_s}\sum_{i=1}^{n} Z_i(c_i * Q_\lambda)(\mathbf{r}).$$

Clearly, Φ_c and Φ_w reflect ionic size effects and nonlocal dielectric effects, respectively.

As a special case, for the local Poisson model (20), we have $\epsilon_\infty = \epsilon_s$ so that

$$\Phi_w(\mathbf{r}) = W(\mathbf{r}), \quad \Phi_c(\mathbf{r}) = \lambda^2\Psi(\mathbf{r}).$$

Hence, a solution of the local Poisson model (20) can be simply expressed in (23).

IV. A NONLOCAL FERMI DISTRIBUTION

In this section, we derive a nonlocal Fermi distribution for an ionic solution containing n different ionic species, and show that it leads to optimal ionic concentrations in the sense of minimizing an electrostatic free energy.

To do so, we consider the boundary value problem (21). Following what is done in [86], we first can show that this boundary value problem has a unique solution W, and the solution can be expressed in the operator form,

$$W = L^{-1}\rho \quad \text{for} \quad \rho \in L^2(\Omega), \tag{27}$$

where L^{-1} denotes the inverse of L, which is a continuous self-adjoint positive linear operator as defined by

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

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 Sobolev space of functions with second-order weak derivatives [87], $(u,v) = \int_\Omega u(\mathbf{r})v(\mathbf{r})d\mathbf{r}$ is an inner product for the Hilbert space $L^2(\Omega)$, which is a set of functions satisfying $(v,v) < \infty$.

Clearly, applying (25) to (27), we can express the solution W of the nonlocal Poisson-Fermi Eq. (21) as a function of ionic concentrations c_i for $i = 1,2,\ldots,n$ in the operator form,

$$W = e_c\sum_{i=1}^{n} Z_i L^{-1}c_i. \tag{28}$$

This shows that different ionic concentrations may result in different potential functions. Hence, it is interesting to search for a set of optimal ionic concentration functions that minimize an electrostatic free energy.

For simplicity, we treat each ion of ionic species i as a hard sphere with radius a_i for $i = 1,2,\ldots,n$, and denote by c_{n+1} as the concentration function of water molecules, and each water molecule is also treated a hard sphere with radius a_{n+1}. Thus, the volume of each ball is given by $4\pi a_i^3/3$. Following [45], we define two void volume fraction functions, Γ^b and $\Gamma(\mathbf{r})$, according to the size constraint conditions,

$$\frac{4\pi}{3}\sum_{i=1}^{n+1} a_i^3 c_i^b + \Gamma^b = 1, \quad \frac{4\pi}{3}\sum_{i=1}^{n+1} a_i^3 c_i(\mathbf{r}) + \Gamma(\mathbf{r}) = 1, \tag{29}$$

where c_i^b denotes the balk concentration of the ith species.

Let $c = (c_1,c_2,\ldots,c_n,c_{n+1})$. We define an electrostatic free energy F as a function of c by

$$F(c) = F_{es}(c) + F_{id}(c) + F_{ex}(c), \tag{30}$$

where F_{es}, F_{id}, and F_{ex} denote the electrostatic, ideal gas, and excess energies, respectively, as follows:

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

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

and

$$F_{ex}(c) = \frac{k_B T}{v_0}\int_\Omega \Gamma(\mathbf{r})\left[\ln\left(\frac{\Gamma(\mathbf{r})}{\Gamma^b}\right) - 1\right]d\mathbf{r}.$$

Here, Γ^b and Γ are given in (29) to be positive, and v_0 denotes a scaling parameter that gives F_{ex} units of energy. Note that v_0 is a constant independent of position. It can be simply set by the formula,

$$v_0 = (8 - 4\pi/3)a^3, \tag{31}$$

which is determined from the case of uniform ionic sizes, i.e., all the radii $a_i = a$ with $a > 0$ for $i = 1,2,\ldots,n+1$. Note that F is a new free energy functional as a modification of the one given in [52, Eq. (10)]. The classic Gibbs free energy functional has been generalized to include all the species—ions, water molecules, and voids—in the same entropy form.

By (28), 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 $F(c)$ along any direction v, which are denoted by $F'(c)v$ and $F''(c)(v,v)$, respectively, as follows:

$$F'(c)v = \sum_{i=1}^{n+1}\int_{D_s}\left[e_c Z_i W + k_B T\ln\left(\frac{c_i}{c_i^b}\right) - k_B T\frac{4\pi a_i^3}{3v_0}\ln\left(\frac{\Gamma(\mathbf{r})}{\Gamma^b}\right)\right]v_i(\mathbf{r})d\mathbf{r},$$

and

$$F''(c)(v,v) = e_c^2\left\langle L^{-1}\sum_{i=1}^{n} Z_i v_i, \sum_{i=1}^{n} Z_i v_i\right\rangle_{L^2(\Omega)} + k_B T\sum_{i=1}^{n+1}\int_{D_s}\frac{1}{c_i}(v_i(\mathbf{r}))^2 d\mathbf{r} + \int_{D_s}\frac{k_B T}{v_0\Gamma(\mathbf{r})}\left(\frac{4\pi}{3}\sum_{i=1}^{n+1} a_i^3 v_i\right)^2 d\mathbf{r}.$$

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

$$e_c Z_i W + k_B T\ln\left(\frac{c_i}{c_i^b}\right) - k_B T\frac{4\pi a_i^3}{3v_0}\ln\left(\frac{\Gamma(\mathbf{r})}{\Gamma^b}\right) = 0, \tag{32}$$

from which we obtain the Fermi distributions,

$$c_i(\mathbf{r}) = c_i^b e^{-\left[\frac{e_c Z_i}{k_B T}W(\mathbf{r}) - \frac{4\pi a_i^3}{3v_0}S^{irc}(\mathbf{r})\right]}, \tag{33}$$

for $i = 1,2,\ldots,n+1$. Here Γ and Γ^b are defined in (29), W is a solution of the nonlocal Poisson-Fermi model (21), v_0 is defined in (31), and S^{trc} is defined by

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

Since $F''(c)$ is strictly positive, the energy functional $F(c)$ has a unique minimizer, which satisfies the Fermi distributions of (33).

The term S^{trc} has been referred to as *a steric potential* since it describes ionic size effects caused by the ionic size constraint conditions (29) [45]. This is the reason why the expression of (33) can be called *a Fermi distribution*. By setting the factor $\frac{4\pi a_i^3}{3v_0} = 1$, our new Fermi distributions (33) can be reduced to the previous ones given in [52, Eq. (7)]. This indicates that our new Fermi distributions have improved the previous ones to better reflect the effects of nonuniform ionic sizes.

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 Eq. (20).

V. A DIMENSIONLESS NONLOCAL POISSON-FERMI MODEL

A combination of (32) and (25) with (21) immediately results in a system of $n+2$ equations for solving the electrostatic potential W and concentration functions $\{c_i\}$ as follows:

$$\begin{aligned} -\epsilon_0\epsilon_s\Delta\left[W - l_c^2\Delta W\right] &= e_c\sum_{i=1}^{n} Z_i c_i(\mathbf{r}), \quad \mathbf{r}\in\Omega, \\ Z_i\frac{e_c}{k_B T}W + \ln\left(\frac{c_i}{c_i^b}\right) - \frac{4\pi}{3v_0}a_i^3\ln\left(\frac{\Gamma(\mathbf{r})}{\Gamma^b}\right) &= 0, \\ \mathbf{r}\in\Omega \quad \text{for } i &= 1,2,\ldots,n+1, \\ W(\mathbf{s}) = g_1(\mathbf{s}), \quad \Delta W(\mathbf{s}) &= g_2(\mathbf{s}), \quad \mathbf{s}\in\partial\Omega, \end{aligned} \tag{34}$$

where $\Gamma(\mathbf{r})$ and Γ^b are given in (29), v_0 is given in (31), $Z_{n+1} = 0$, and $l_c^2 = \frac{\epsilon_\infty}{\epsilon_s}\lambda^2$.

In biomolecular simulations, 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:

$$\Gamma(\mathbf{r}) = 1 - \frac{4\pi N_A}{3\times 10^{27}}\sum_{i=1}^{n+1} a_i^3 c_i(\mathbf{r}), \tag{35a}$$

$$\Gamma^b = 1 - \frac{4\pi N_A}{3\times 10^{27}}\sum_{i=1}^{n+1} a_i^3 c_i^b. \tag{35b}$$

Furthermore, by the variable changes,

$$u = \frac{e_c}{k_B T}W,$$

the nonlocal Poisson-Fermi model (34) can be reformulated into the dimensionless form,

$$\begin{aligned} -\epsilon_s\Delta\left[u - l_c^2\Delta u\right] &= \frac{e_c^2 N_A}{\epsilon_0 k_B T 10^{17}}\sum_{i=1}^{n} Z_i c_i \quad \text{in} \quad \Omega, \\ u(\mathbf{s}) = \frac{e_c}{k_B T}g_1(\mathbf{s}), \quad \Delta u(\mathbf{s}) &= \frac{e_c}{k_B T}g_2(\mathbf{s}), \\ \mathbf{s}\in\partial\Omega, \end{aligned} \tag{36}$$

subject to the $n+1$ nonlinear algebraic equations:

$$Z_i u + \ln(c_i) - \frac{4\pi a_i^3}{3v_0}\ln\Gamma(\mathbf{r}) = \ln\left(c_i^b\right) - \frac{4\pi a_i^3}{3v_0}\ln(\Gamma^b), \tag{37}$$

for $i = 1,2,\ldots,n+1$ in Ω. Here, $\Gamma(\mathbf{r})$ and Γ^b are given in (35), c_i and c_i^b are in moles per liter, and u gives an electrostatic potential in units of $e_c/(k_B T)$.

From the definition of each algebraic equation of (37) it can be seen that both Γ^b and $\Gamma(\mathbf{r})$ must be positive. By a proper selection of bulk concentrations, the requirement that $\Gamma^b > 0$ can be easily satisfied. However, ensuring that $\Gamma(\mathbf{r}) > 0$ in an approximation method for solving the Poisson-Fermi model (36) is of great concern, which may cause numerical stability problems in practical implementation.

As initial study, we obtain a sufficient condition that guarantees $\Gamma(\mathbf{r}) > 0$ to hold for each $\mathbf{r}$ in Ω as follows:

$$0 < c_j(\mathbf{r}) < \frac{3\times 10^{27}}{4\pi N_A\sum_{i=1}^{n+1} a_i^3}, \quad j = 1,2,\ldots,n+1. \tag{38}$$

To get a boundedness condition for the potential function u under the above condition, we reformulate each algebraic equation of (37) as

$$c_i(\mathbf{r}) = c_i^b(\Gamma^b)^{-\frac{4\pi a_i^3}{3v_0}}(\Gamma(\mathbf{r}))^{\frac{4\pi a_i^3}{3v_0}}e^{-Z_i u(\mathbf{r})}.$$

Since $\Gamma(\mathbf{r}) < 1$, from the above identity we can get another upper bound of c_i in terms of u,

$$c_i(\mathbf{r}) \leqslant c_i^b(\Gamma^b)^{-\frac{4\pi a_i^3}{3v_0}}e^{-Z_i u(\mathbf{r})}, \quad i = 1,2,\ldots,n, \tag{39}$$

showing that a value range of each ionic concentration function is mainly determined by the value range of potential function. Hence, a combination of (38) with (39) results in a sufficient condition for u to satisfy,

$$c_i^b(\Gamma^b)^{-\frac{4\pi a_i^3}{3v_0}}e^{-Z_i u} \leqslant \frac{3\times 10^{27}}{4\pi N_A\sum_{i=1}^{n+1} a_i^3}, \quad i = 1,2,\cdots,n, \tag{40}$$

to ensure that $\Gamma(\mathbf{r}) > 0$. The above condition can be used to estimate a value range of potential function under the requirement that $\Gamma(\mathbf{r}) > 0$ in the solvent domain Ω.

VI. NUMERICAL TESTS

The boundedness conditions (38) and (40) are particularly valuable in the study of numerical stability for an iterative algorithm used to compute electrostatic potential function and ionic concentrations. To illustrate this issue, we compare the nonlocal Poisson model (11) and Poisson-Fermi model (36) for a NaCl electrolyte in terms of their solution ranges. The smaller the range of the potential function is, the better the model, since the model with a smaller solution range can satisfy the boundedness conditions (38) and (40) relatively easier.

Figure 2 shows that the value range of convolution function W in the bottom plot is

$$-0.4363 \leqslant W(\mathbf{r}) \leqslant -0.2273, \quad \mathbf{r} \in \Omega,$$

which is considerably smaller than that of potential function Φ as shown in the top plot:

$$-37.7190 \leqslant \Phi \leqslant -1.2484, \quad \mathbf{r} \in \Omega.$$

Here, Φ is a solution of a nonlocal Poisson test model (called Model 1 in Xie *et al.*'s recent work [88]), and W is the convolution of Φ with the Yukawa-like kernel Q_λ.

We also calculated the bounds of conditions (38) and (40) for the NaCl electrolyte. Here, we set $n = 2$, $Z_1 = 1$, $Z_2 = -1$, $a_1 = 0.95$, $a_2 = 1.81$, and $a_3 = 1.4$ as the radii of Na^+, Cl^-, and water molecule H_2O, respectively [46]. By (38), an upper bound for all the three concentrations was found as

$$0 < c_i(\mathbf{r}) < 41.6, \quad \mathbf{r} \in \Omega, \quad \text{for} \quad i = 1,2,3. \tag{41}$$

Using (40), we then found a value range of u as

$$-4.8 < u < 1.4, \tag{42}$$

for the case that $\Gamma^b = 0.2$, $v_0 = 10$, and $c_1^b = c_2^b = 0.2$.

As shown in Sec. III, our nonlocal Poisson-Fermi model is a convolution of the corresponding nonlocal Poisson model. Hence, the above numerical results illustrate that a Poisson-Fermi model can be better than its corresponding Poisson model.

Finally, some details of the protein tests for Fig. 2 are given here. The protein was downloaded from the Protein Data Bank (PDB, http://www.rcsb.org) with the PDB ID: 2LZX. The solvent region $\Omega = (-2, -2)^3 \setminus D_p$ with $D_p = \{\mathbf{r} \mid |\mathbf{r}| < 1\}$. The 488 atomic charges from the protein were scaled to the unit ball D_p such that each charge position had a length less than 0.8. The potentials Φ and W were calculated by using their series expressions given in [88], 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 using 100 terms. In the tests, we set $\epsilon_p = 2$, $\epsilon_s = 80$, $\epsilon_\infty = 1.8$, and $\lambda = 10$. The physical parameter values of ϵ_0, e_c, T, and k_B given in [88] were used.

VII. CONCLUSIONS

Ions always interact in water solutions, because ions are charged and water has strong electric fields (although the net charge of a water molecule is zero). In chemical language, ions interact in polar solvents (like water), which have a nonvanishing dipole moment. The interactions of ions and water and the interactions of ions with each other have been studied extensively, first treating ions as point charges. 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 propose a new Poisson-Fermi model for ionic solvent using Xie *et al.*'s nonlocal Poisson dielectric theory. Its solution is found to be a convolution of the solution of a nonlocal Poisson dielectric model with a Yukawa-like kernel function. It also remarkably leads to a new decomposition of an electrostatic potential with one component function for nonlocal dielectric effects and the other for ionic size effects. We then obtain a new formula for estimating the nonlocal parameter λ in the spirit of the Debye length, which depends on (and varies with) the ionic strength and individual concentrations of ions present in ionic mixtures like biological solutions and seawater. This is very different from Santangelo's model [71] in which the parameter is a correlation length that is not specifically related to ionic strength and hence does not change with ionic concentrations in the bulk solution. Furthermore, we construct a new electrostatic free energy and prove it to have a unique minimizer. After the minimization of this electrostatic free energy, we derive a new nonlocal Fermi distribution for a mixture of spherical ions and water molecules with different radii. Our Fermi distribution and the corresponding free energy functional are different from those derived by Liu and Eisenberg even though they similarly use the specific ionic radii associated with a steric potential and the interstitial voids among bio-ions and water molecules. A combination of our Poisson-Fermi model with this new Fermi distribution leads to our new nonlocal Poisson Fermi model for computing both the convolution of electrostatic potential and ionic concentrations. In addition, we find that ionic concentrations have a limited range when they are placed in the Fermi-Poisson model. They cannot overfill space. This treatment of saturation of concentration well illustrates why the Poisson-Fermi approach is more favorable than the classic Poisson approach: Ionic concentrations are very large, approaching saturation, in many biological and technological applications involving ionic solutions. The new approach may also improve stability and convergence as we implement the model numerically for real applications, involving nonuniform sizes, nonlocal dielectric properties, and nearly saturating concentrations in crucial locations, and much smaller concentrations elsewhere. Our numerical results indeed show that the Poisson-Fermi approach is numerically more stable. They encourage us to further study the nonlocal Poisson-Fermi model theoretically and numerically in the future. Following what was done in [45,46], we plan to validate our nonlocal Poisson-Fermi model using experimental data on bulk solutions and later on ion channels.

Later work will examine how well the nonlocal Poisson Fermi model fits experimental data. Moreover, this new model will be adopted to the study of biomolecules (e.g., nucleic acids and proteins, including ion channels,) and biological applications that involve ionic flows and concentrated ionic mixtures, and will be compared to Liu and

Eisenberg's Poisson-Fermi and Poisson-Nernst-Planck-Fermi (PNPF) models, which themselves did surprisingly well describing bulk solutions [46], and the gramicidin and L-type calcium channels [45].

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