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A new analysis of electrostatic free energy minimization and Poisson–Boltzmann equation for protein in ionic solvent☆

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HIGHLIGHTS

- Give Poisson dielectric model a solution splitting formula and prove it to have a unique solution.
- Present a new modified electrostatic free energy minimization problem for protein in ionic solvent.
- Find the first and second Gâteaux derivatives of the target function of the new minimization problem.
- Prove the new modified electrostatic free energy minimization problem to have a unique solution.
- Prove solution equivalence between the new minimization problem and Poisson–Boltzmann equation.

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ABSTRACT

In this paper, a novel solution decomposition of the Poisson dielectric model is proposed to modify a traditional electrostatic free energy minimization problem into one that is well defined for the case of protein in ionic solvent. The target function of this modified problem is shown to be strictly convex, weak sequentially lower semicontinuous, and twice continuously Fréchet differentiable. Its first and second Gâteaux derivatives are then found. Moreover, it is proved that this modified electrostatic free energy minimization problem has a unique solution, and its solution existence and uniqueness is equivalent to that of the Poisson–Boltzmann equation, a widely-used implicit solvent model for computing the electrostatics of biomolecules.

1. Introduction

Electrostatic potential energy plays essential roles in the structure and biological function of proteins, catalytic activity, and ligand association [1–4]. One mathematical model commonly used for estimating the electrostatic potential function $\Phi(\mathbf{r})$ in an ionic solvent is the Poisson–Boltzmann equation (PBE), which has been widely employed in many important bioengineering applications, such as protein docking, ion channel modeling, and rational drug design [5–8]. In mathematics, PBE is a second order nonlinear elliptic partial differential equation with jump discontinuous coefficients and singular

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distribution source terms over the whole space $\mathbb{R}^3$. It was claimed for a long time that the traditional electrostatic free energy minimization problem has a unique solution, and the PBE solution gives an equilibrium electrostatic potential generated from this traditional minimization problem, but a rigorous verification of this claim is difficult due to singularities caused by atomic point charges from the protein molecule. Here each point charge is represented by a Dirac delta distribution.

Clearly, the traditional electrostatic free energy minimization problem can be viewed as a Poisson dielectric model constrained minimization problem (see (3)). Thus, its analysis seems to be able to be done by using regular variational techniques. Unfortunately, these techniques would not work because this traditional problem becomes a poorly defined one in the case of proteins in ionic solvent. In fact, in this case, the Poisson dielectric model has a singular solution, which makes the target functional of this traditional problem to become undefined on any function space, and not to have any variations or Gâteaux derivatives. In the early work (see [9] and its references 3 to 10 for example), the first and second variations were calculated only symbolically.

To improve the early work, recently, a modified electrostatic free energy minimization problem was employed to substitute the traditional electrostatic free energy minimization problem [10, see (1.2)]. Although it is a well defined one, its definition still involved the singular solution of the Poisson dielectric model. To deal with the related singularity difficulties, very weak function spaces (e.g., $H^1_*(\Omega)$ and $[L^1(\Omega) \cap H^{-1}(\Omega)]^n$ given in [10, Pages 2541–2542]) were selected, resulting in a complicated analysis [10].

As a continuation of these early efforts, in this paper, we propose to split the solution Φ of the Poisson dielectric model as a sum of three component functions, G, Ψ, and $\tilde{\Phi}$, according to the potential contributions from the biomolecular charges, the biomolecular interface, and the ionic solvent charges (see Lemma 3.1). Since G collects all the singular points of Φ, Ψ and $\tilde{\Phi}$ are proved to be two sufficiently smooth functions (see Theorem 3.2). As a result, the variational problem of $\tilde{\Phi}$ is able to be reformulated as an operator equation in terms of a self-adjoint, strictly positive, and invertible linear operator L (see Theorem 3.3) so that $\tilde{\Phi}$ (not Φ) is expressed as a function of ionic concentrations (see (23)). In this way, we modify the traditional electrostatic free energy minimization problem into one that is well defined (see (32)). We show that the target functional f (see (28)) of this new modified problem is strictly convex, weak sequentially lower semicontinuous, and twice continuously Fréchet differentiable. We then find the first and second Gâteaux derivatives of f, and prove that this new modified problem has a unique solution satisfying the Euler equation (see Theorem 5.3). Moreover, we show that PBE is a reduced form of the Euler equation, and its solution existence and uniqueness is equivalent to that of our modified electrostatic free energy minimization problem (see Corollary 5.4).

Finally, we point out that our solution decomposition has been used to overcome the difficulty of computing the energy term $\langle \delta_{\mathbf{r}_j}, \Phi \rangle$ in this paper. Here $\mathbf{r}_j$ denotes the position of the jth atom of a protein, and $\delta_{\mathbf{r}_j}$ is the Dirac delta distribution at $\mathbf{r}_j$. It is known that $\langle \delta_{\mathbf{r}_j}, \Phi \rangle$ is defined as $\Phi(\mathbf{r}_j)$ if a value of $\Phi(\mathbf{r}_j)$ exists. However, in the protein case, the singularity of $\Phi(\mathbf{r})$ at $\mathbf{r}_j$ makes $\Phi(\mathbf{r}_j)$ infinite. To deal with this blow-up problem, in the current literature, $\langle \delta_{\mathbf{r}_j}, \Phi \rangle$ is commonly approximated by

$$\langle \delta_{\mathbf{r}_j}, \Phi \rangle \approx \int_\Omega \delta_h(\mathbf{r} - \mathbf{r}_j)\Phi_h(\mathbf{r})d\mathbf{r},$$

where $\delta_h(\mathbf{r} - \mathbf{r}_j)$ denotes an approximate function of $\delta_{\mathbf{r}_j}$, and Φ_h is a numerical solution of the PBE model calculated by using $\delta_h(\mathbf{r} - \mathbf{r}_j)$ to replace $\delta_{\mathbf{r}_j}$. In this paper, we have redefined $\Phi(\mathbf{r}_j)$ with a well defined value (see (24)) according to our solution decomposition. This new definition of $\Phi(\mathbf{r}_j)$ is valuable in mathematical analysis though it may not change any physical property predicted by PBE since the singular energy terms caused by the Dirac delta distributions can be removed through considering electrostatic free energy differences [11].

The remaining sections of the paper are outlined as follows. In Section 2, we review the PBE model and the traditional electrostatic free energy minimization problem. In Section 3, we present the solution decomposition formula, and use it to analyze the Poisson dielectric model. In Section 4, we define our new modified minimization problem. Finally, the analysis of our new minimization problem is reported in Section 5.

2. PBE and traditional free energy minimization problem

In this section we present the definitions of PBE, the Poisson dielectric model, and the traditional electrostatic free energy minimization problem based on the following domain partition of the whole space $\mathbb{R}^3$

$$\mathbb{R}^3 = D_p \cup D_s \cup \Gamma,$$

where D_p is a bounded region hosting a protein, D_s denotes the solvent region surrounding D_p, and Γ is the interface between D_p and D_s. See Fig. 1 for an illustration. Here the solvent contains n different species of ions with q_i and c_i being the charge and the ionic concentration function of species i for $i = 1, 2, \ldots, n$, and the protein consists of n_p atoms with $\mathbf{r}_j$ and Q_j being the position and charge of the jth atom, respectively, for $j = 1, 2, \ldots, n_p$. As an implicit solvent approach [5], both the protein region D_p and solvent region D_s are treated as two continuum media with two different positive dielectric constants, ϵ_p and ϵ_s, satisfying $\epsilon_p < \epsilon_s$, respectively.

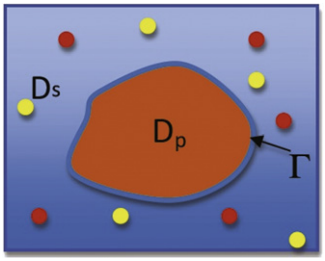

Fig. 1. An illustration on a protein region D_p surrounded by the ionic solvent region D_s with interface Γ. Here two different species of ions are colored in red and yellow, respectively.

By the above notation, the PBE model for protein in ionic solvent is defined as a nonlinear elliptic interface problem as follows:

$$\begin{cases} -\epsilon_p \Delta\Phi(\mathbf{r}) = 4\pi \sum_{j=1}^{n_p} Q_j \delta_{\mathbf{r}_j}, & \mathbf{r} \in D_p, \\ -\epsilon_s \Delta\Phi(\mathbf{r}) = 4\pi \sum_{i=1}^{n} q_i M_i e^{-\beta q_i \Phi}, & \mathbf{r} \in D_s, \\ \Phi(\mathbf{s}^+) = \Phi(\mathbf{s}^-), \quad \varepsilon_s \dfrac{\partial \Phi(\mathbf{s}^+)}{\partial \mathbf{n}(\mathbf{s})} = \varepsilon_p \dfrac{\partial \Phi(\mathbf{s}^-)}{\partial \mathbf{n}(\mathbf{s})}, & \mathbf{s} \in \Gamma, \\ \Phi(\mathbf{r}) \to 0 & \text{as } |\mathbf{r}| \to \infty, \end{cases} \tag{1}$$

where $\delta_{\mathbf{r}_j}$ is the Dirac delta distribution, β and M_i are given by

$$\beta = 1/(k_B T), \qquad M_i = \Lambda_i^{-3} e^{\beta \mu_i}, \tag{2}$$

with k_B being the Boltzmann constant, T the absolute temperature, Λ_i the thermal de Broglie wavelength of ionic species i, μ_i the chemical potential of ionic species i, and $\mathbf{n}(\mathbf{s})$ denotes the unit outward normal vector of D_p. As a continuous linear functional, $\delta_{\mathbf{r}_j}(v)$ is also written as $\delta_{\mathbf{r}_j}(v) = \langle \delta_{\mathbf{r}_j}, v \rangle$ [12].

In the study of the PBE model, the following traditional constrained electrostatic free energy minimization problem is often considered:

$$\min\{F(\Phi, c) | (\Phi, c) \in U \times V\}, \tag{3}$$

subject to the Poisson dielectric model

$$\begin{cases} -\epsilon_p \Delta\Phi(\mathbf{r}) = \rho(\mathbf{r}), & \mathbf{r} \in D_p, \\ -\epsilon_s \Delta\Phi(\mathbf{r}) = 4\pi \sum_{i=1}^{n} q_i c_i(\mathbf{r}), & \mathbf{r} \in D_s, \\ \Phi(\mathbf{s}^+) = \Phi(\mathbf{s}^-), \quad \varepsilon_s \dfrac{\partial \Phi(\mathbf{s}^+)}{\partial \mathbf{n}(\mathbf{s})} = \varepsilon_p \dfrac{\partial \Phi(\mathbf{s}^-)}{\partial \mathbf{n}(\mathbf{s})}, & \mathbf{s} \in \Gamma, \\ \Phi(\mathbf{r}) \to 0 & \text{as } |\mathbf{r}| \to \infty, \end{cases} \tag{4}$$

where $c = (c_1, c_2, \ldots, c_n)$, U and V denote two function spaces, ρ_p denotes a charge density function within the protein region D_p, and $F(\Phi, c)$ is an electrostatic free energy functional given by

$$F(\Phi, c) = F_{es}(\Phi, c) + F_{id}(c) + F_G(c), \tag{5}$$

with F_{es}, F_{id}, and F_G being the energy terms from electrostatics, ideal gas, and Gibbs free energy contributions, respectively, as follows:

$$F_{es}(\Phi, c) = \frac{1}{2} \int_{\mathbb{R}^3} \rho(\mathbf{r}) \Phi(\mathbf{r}) d\mathbf{r}, \tag{6}$$

$$F_{id}(c) = \frac{1}{\beta} \sum_{i=1}^{n} \int_{D_s} c_i(\mathbf{r}) [\ln(c_i(\mathbf{r}) \Lambda_i^3) - 1] d\mathbf{r}, \qquad F_G(c) = -\sum_{i=1}^{n} \mu_i \int_{D_s} c_i(\mathbf{r}) d\mathbf{r}. \tag{7}$$

Here ρ denotes the total charge density function given by

$$\rho = \rho_p + \sum_{i=1}^{n} q_i c_i,$$

and each c_i has been extended as zero in D_p for the convenience. However, in the case of a protein in an ionic solvent, $\rho_p = \sum_{j=1}^{n_p} Q_j \delta_{\mathbf{r}_j}$. Substituting it to (6) gives

$$F_{es}(\Phi, c) = \frac{1}{2}\sum_{j=1}^{n_p} Q_j \Phi(\mathbf{r}_j) + \frac{1}{2}\sum_{i=1}^{n} q_i \int_{D_s} c_i(\mathbf{r})\Phi(\mathbf{r})d\mathbf{r}. \tag{8}$$

Clearly, the above expression becomes undefined due to that Φ has singularities at the atomic positions $\mathbf{r}_j$ (as shown in the next section). Thus, some modifications must be done on the definition of F_{es}.

3. Solution decomposition and Poisson dielectric model analysis

In this section, we propose a solution decomposition for the Poisson dielectric model (4) in Lemma 3.1, and use it to prove the solution existence and uniqueness of the Poisson dielectric model (4) in Theorem 3.2.

Lemma 3.1. *Let Φ be the solution of the Poisson dielectric model (4). Then Φ can be decomposed as*

$$\Phi = \tilde{\Phi} + \Psi + G, \tag{9}$$

where $\tilde{\Phi}$ is the solution of the exterior charge Poisson dielectric model

$$\begin{cases} -\Delta\tilde{\Phi}(\mathbf{r}) = 0, & \mathbf{r} \in D_p, \\ -\epsilon_s \Delta\tilde{\Phi}(\mathbf{r}) = 4\pi \sum_{i=1}^{n} q_i c_i(\mathbf{r}), & \mathbf{r} \in D_s, \\ \tilde{\Phi}(\mathbf{s}^+) = \tilde{\Phi}(\mathbf{s}^-), \quad \varepsilon_s \dfrac{\partial\tilde{\Phi}(\mathbf{s}^+)}{\partial\mathbf{n}(\mathbf{s})} = \varepsilon_p \dfrac{\partial\tilde{\Phi}(\mathbf{s}^-)}{\partial\mathbf{n}(\mathbf{s})}, & \mathbf{s} \in \Gamma, \\ \tilde{\Phi}(\mathbf{r}) \to 0 & \text{as } |\mathbf{r}| \to \infty, \end{cases} \tag{10}$$

Ψ is the solution of the interface charge Poisson dielectric model

$$\begin{cases} \Delta\Psi(\mathbf{r}) = 0, & \mathbf{r} \in D_p \cup D_s, \\ \Psi(\mathbf{s}^+) = \Psi(\mathbf{s}^-), & \mathbf{s} \in \Gamma, \\ \varepsilon_s \dfrac{\partial\Psi(\mathbf{s}^+)}{\partial\mathbf{n}(\mathbf{s})} = \varepsilon_p \dfrac{\partial\Psi(\mathbf{s}^-)}{\partial\mathbf{n}(\mathbf{s})} + (\epsilon_p - \epsilon_s)\dfrac{\partial G(\mathbf{s})}{\partial\mathbf{n}(\mathbf{s})}, & \mathbf{s} \in \Gamma, \\ \Psi(\mathbf{r}) \to 0 & \text{as } |\mathbf{r}| \to \infty, \end{cases} \tag{11}$$

and G is a known function as given by

$$G(\mathbf{r}) = \frac{1}{\epsilon_p}\sum_{j=1}^{n_p} \frac{Q_j}{|\mathbf{r} - \mathbf{r}_j|}. \tag{12}$$

Here $\frac{\partial G(\mathbf{s})}{\partial\mathbf{n}(\mathbf{s})}$ can be found in the form

$$\frac{\partial G(\mathbf{s})}{\partial\mathbf{n}(\mathbf{s})} = -\frac{1}{\varepsilon_p}\sum_{j=1}^{n_p} Q_j \frac{(\mathbf{s} - \mathbf{r}_j)\cdot\mathbf{n}}{|\mathbf{s} - \mathbf{r}_j|^3}. \tag{13}$$

Proof. Since $\frac{1}{4\pi|\mathbf{r}-\mathbf{r}_j|}$ satisfies the equation $-\Delta G_j = \delta_{\mathbf{r}_j}$ [13, Page 111],

$$\Delta G = \frac{4\pi}{\epsilon_p}\sum_{j=1}^{n_p} Q_j \Delta \frac{1}{4\pi|\mathbf{r} - \mathbf{r}_j|} = -\frac{4\pi}{\epsilon_p}\sum_{j=1}^{n_p} Q_j \delta_{\mathbf{r}_j}.$$

For $\mathbf{r} \in D_p$, we have $\Delta\Psi = 0$ and $\Delta\tilde{\Phi} = 0$. Thus,

$$\Delta\Phi = \Delta\tilde{\Phi} + \Delta\Psi + \Delta G = -\frac{4\pi}{\varepsilon_p}\sum_{j=1}^{n_p} Q_j \delta_{\mathbf{r}_j} \quad \text{in } D_p.$$

Similarly, we can verify $\Delta\Phi = -\frac{4\pi}{\epsilon_s}\sum_{i=1}^{n} q_i c_i(\mathbf{r})$ for $\mathbf{r} \in D_s$ since $\Delta G = 0$ in D_s.

On the interface Γ, $\tilde{\Phi}$ and Ψ satisfy the interface conditions given in (10) and (11), respectively, while both $G(\mathbf{s})$ and $\frac{\partial G(\mathbf{s})}{\partial \mathbf{n}(\mathbf{s})}$ are continuous. As a result, we have

$$\begin{aligned}
&\Phi(s^+) = \tilde{\Phi}(s^+) + \Psi(s^+) + G(s) = \tilde{\Phi}(s^-) + \Psi(s^-) + G(s) = \Phi(s^-) \quad \forall \mathbf{s} \in \Gamma,\\
&\epsilon_p \frac{\partial \Phi(s^-)}{\partial \mathbf{n}(\mathbf{s})} = \epsilon_p \frac{\partial \tilde{\Phi}(s^-)}{\partial \mathbf{n}(\mathbf{s})} + \epsilon_p \frac{\partial \Psi(s^-)}{\partial \mathbf{n}(\mathbf{s})} + \epsilon_p \frac{\partial G(s)}{\partial \mathbf{n}(\mathbf{s})}\\
&\qquad = \epsilon_s \frac{\partial \tilde{\Phi}(s^+)}{\partial \mathbf{n}(\mathbf{s})} + \epsilon_s \frac{\partial \Psi(s^+)}{\partial \mathbf{n}(\mathbf{s})} - (\epsilon_p - \epsilon_s) \frac{\partial G(\mathbf{s})}{\partial \mathbf{n}(\mathbf{s})} + \epsilon_p \frac{\partial G(s)}{\partial \mathbf{n}(\mathbf{s})}\\
&\qquad = \epsilon_s \frac{\partial}{\partial \mathbf{n}(\mathbf{s})} (\tilde{\Phi} + \Psi + G)(s^+) = \epsilon_s \frac{\partial \Phi(s^+)}{\partial \mathbf{n}(\mathbf{s})} \quad \forall \mathbf{s} \in \Gamma.
\end{aligned}$$

Finally, it is obvious that $\Phi(\mathbf{r}) = \tilde{\Phi}(\mathbf{r}) + \Psi(\mathbf{r}) + G(\mathbf{r}) \to 0$ as $|\mathbf{r}| \to \infty$.

We next consider the solution existence and uniqueness of the Poisson dielectric model (4). For simplicity, we modify (4), (10) and (11), respectively, as three boundary value problems using the following homogeneous Dirichlet boundary conditions:

$$\Phi(\mathbf{s}) = 0, \qquad \tilde{\Phi}(\mathbf{s}) = 0, \qquad \Psi(\mathbf{s}) = 0 \quad \forall \mathbf{s} \in \partial\Omega, \tag{14}$$

where Ω is a sufficiently large sphere. In this case of approximation, D_s is set as $D_s = \Omega \setminus (D_p \cup \Gamma)$. An inhomogeneous Dirichlet boundary condition can also be constructed by using numerical techniques from [14,11] for example, and can be treated similarly as what is done in [15] for the analysis.

By the first Green's formula, it is easy to get the weak forms of the two boundary value problems of Ψ and $\tilde{\Phi}$ as follows:

$$a(\tilde{\Phi}, v) = b(v) \quad \forall v \in H_0^1(\Omega), \tag{15}$$

and

$$a(\Psi, v) = (\epsilon_s - \epsilon_p) \int_\Gamma \frac{\partial G(\mathbf{s})}{\partial \mathbf{n}(\mathbf{s})} v(\mathbf{s}) d\mathbf{s} \quad \forall v \in H_0^1(\Omega), \tag{16}$$

where $a(u, v)$ and $b(v)$ are defined by

$$a(u, v) = \epsilon_p \int_{D_p} \nabla u \cdot \nabla v d\mathbf{r} + \epsilon_s \int_{D_s} \nabla u \cdot \nabla v d\mathbf{r}, \qquad b(v) = 4\pi \sum_{i=1}^{n} q_i \int_{D_s} c_i v d\mathbf{r}, \tag{17}$$

$H_0^1(\Omega)$ is the usual Sobolev function space with the norm

$$\|v\|_{H^1(\Omega)} = \left(\|v\|^2_{L^2(\Omega)} + \|\nabla v\|^2_{L^2(\Omega)} \right)^{1/2} \quad \forall v \in H_0^1(\Omega),$$

and $\|v\|_{L^2(\Omega)}$ is set as

$$\|v\|_{L^2(\Omega)} = \left(\int_\Omega |v(\mathbf{r})|^2 d\mathbf{r} \right)^{1/2}.$$

The solution existence and uniqueness for the Poisson dielectric model (4), the exterior charge Poisson dielectric model (10), and the interface charge Poisson dielectric model (11) with the boundary value conditions in (14) are presented in the following theorem.

Theorem 3.2. *Let $U = H_0^1(\Omega) \cap H^2(D_p) \cap H^2(D_s)$ and its norm be defined by*

$$\|v\|_U = \|v\|_{H^1(\Omega)} + \|v\|_{H^2(D_p)} + \|v\|_{H^2(D_s)}.$$

If the interface Γ is of class C^2, and $c_i \in L^2(\Omega)$ for $i = 1, 2, \ldots, n$, then the weak forms (15) and (16) have unique solutions $\tilde{\Phi}$ and Ψ in U, and there exist positive constants C_1 and C_2 such that

$$\|\tilde{\Phi}\|_U \le C_1 \sum_{i=1}^{n} |q_i| \|c_i\|_{L^2(\Omega)}, \qquad \|\Psi\|_U \le C_2 (\epsilon_s - \epsilon_p) \left\| \frac{\partial G}{\partial \mathbf{n}} \right\|_{H^{\frac{1}{2}}(\Gamma)}, \tag{18}$$

where G and $\frac{\partial G(\mathbf{s})}{\partial \mathbf{n}}$ are given in (12) and (13).

Moreover, the Poisson dielectric model (4) has a unique weak solution Φ.

Proof. From (17) it is seen that $a(u, v)$ is a bilinear functional on $H_0^1(\Omega)$, and $b(v)$ is a linear bounded functional on $H_0^1(\Omega)$ for each $c_i \in L^2(\Omega)$. By $0 < \epsilon_p < \epsilon_s$ and Schwarz's inequality, the continuity of $a(u, v)$ is shown as follows:

$$\begin{aligned}
|a(u, v)| &\le (\epsilon_p + \epsilon_s) \int_\Omega |\nabla u \cdot \nabla v| d\mathbf{r}\\
&\le 2\epsilon_s \|\nabla u\|_{L^2(\Omega)} \|\nabla v\|_{L^2(\Omega)} \le 2\epsilon_s \|u\|_{H^1(\Omega)} \|v\|_{H^1(\Omega)}.
\end{aligned} \tag{19}$$

Using Poincare's inequality [15, Page 62], we get the coercivity of $a(u, v)$:

$$\begin{aligned} a(v, v) &= \epsilon_p \int_{D_p} |\nabla v|^2 d\mathbf{r} + \epsilon_s \int_{D_s} |\nabla v|^2 d\mathbf{r} \\ &\geq \epsilon_p \int_{\Omega} |\nabla v|^2 d\mathbf{r} \geq \frac{\epsilon_p}{C} \|v\|^2_{H^1(\Omega)} \quad \forall v \in H^1_0(\Omega), \end{aligned} \tag{20}$$

where C is a positive constant. Since G is smooth in D_s, $\|\nabla G\|_{L^2(D_s)}$ is bounded. Thus, the right hand side term of (16) is a bounded linear functional on $H^1_0(\Omega)$ as shown below:

$$\left| \int_{\Gamma} \frac{\partial G(\mathbf{s})}{\partial \mathbf{n}(\mathbf{s})} v(\mathbf{s}) d\mathbf{s} \right| = \left| \int_{D_s} \nabla G \cdot \nabla v d\mathbf{r} \right| \leq \|\nabla G\|_{L^2(D_s)} \|v\|_{H^1(\Omega)},$$

where the fact $\Delta G = 0$ in D_s has been used.

Hence, using the Lax–Milgram lemma [16], we claim that both (15) and (16) have unique solutions in $H^1_0(\Omega)$.

Furthermore, we claim that the solutions $\tilde{\Phi}$ and Ψ of (15) and (16) are in U, and satisfy (18) according to the regularity analysis of a general interface problem given in [17, Theorem 2.1] (or see [18,19]) and Minkowski's Inequality (see [15, (1.1.3)]), since we have $\sum_{i=1}^{n} q_i c_i \in L^2(\Omega)$ and $\frac{\partial G}{\partial \mathbf{n}} \in H^{\frac{1}{2}}(\Gamma)$ due to that $c_i \in L^2(\Omega)$ and $\frac{\partial G(\mathbf{s})}{\partial \mathbf{n}(\mathbf{s})}$ is smooth on Γ.

Finally, the solution decomposition (9) immediately gives that (4) has a unique weak solution Φ. This completes the proof.

With the bilinear functional $a(\cdot, \cdot)$ given in (17), we define a linear operator $L : U \to L^2(\Omega)$ by

$$\langle Lu, v \rangle_{L^2(\Omega)} = a(u, v) \quad \forall u, v \in U. \tag{21}$$

The properties of L are presented in Theorem 3.3. The proof of Theorem 3.3 is straightforward. It is omitted here.

Theorem 3.3. *Let $U = H^1_0(\Omega) \cap H^2(D_p) \cap H^2(D_s)$. If L is defined in (21), then L is a continuous self-adjoint positive linear operator on U. Moreover, its inverse L^{-1} exists and is a continuous self-adjoint positive linear operator.*

From the definition of L in (21) we can see that the weak form (15) can be expressed as

$$\langle L\tilde{\Phi}, v \rangle_{L^2(\Omega)} = \left\langle 4\pi \sum_{i=1}^{n} q_i c_i, v \right\rangle_{L^2(\Omega)} \quad \forall v \in U,$$

or equivalently the operator equation

$$L\tilde{\Phi} = 4\pi \sum_{i=1}^{n} q_i c_i \quad \text{on } L^2(\Omega). \tag{22}$$

We then use Theorem 3.3 to express $\tilde{\Phi}$ explicitly as a function of c in the form

$$\tilde{\Phi}(c) = 4\pi \sum_{i=1}^{n} q_i L^{-1} c_i \quad \forall c_i \in L^2(\Omega). \tag{23}$$

From the solution decomposition (9) it can be seen that the solution Φ of the Poisson dielectric model (4) has singular points at $\mathbf{r}_j$ for $j = 1, 2, \ldots, n_p$. Thus, the expression (8) of the electrostatic energy term F_{es} becomes undefined, causing the traditional electrostatic free energy minimization problem (3) to become a poor minimization problem. Hence, the traditional minimization problem (3) must be modified before carrying out any mathematical analysis.

4. Our modified electrostatic free energy minimization problem

In this section, we present our modified electrostatic free energy minimization problem. The key step is to modify the electrostatic free energy term F_{es} of (8) by our solution decomposition (9).

We first redefine the value of $\Phi(\mathbf{r}_j)$ by

$$\Phi(\mathbf{r}_j) = \tilde{\Phi}(\mathbf{r}_j) + \Psi(\mathbf{r}_j) + \tilde{G}(\mathbf{r}_j), \quad j = 1, 2, \ldots, n_p, \tag{24}$$

where $\tilde{G}(\mathbf{r}_j)$ is a direct modification of the singular term $G(\mathbf{r}_j)$ as given below

$$\tilde{G}(\mathbf{r}_j) = \frac{1}{\epsilon_p} \sum_{i=1, i\neq j}^{n_p} \frac{Q_i}{|\mathbf{r}_j - \mathbf{r}_i|} \quad \text{for } j = 1, 2, \ldots, n_p, \tag{25}$$

in which all the self-reaction terms of $G(\mathbf{r}_j)$ have been removed. Such a modification is necessary since in Physics a single point charge is prohibited to react with itself. Note that $\tilde{\Phi}(\mathbf{r}_j)$ and $\Psi(\mathbf{r}_j)$ are well defined for any $\mathbf{r}_j \in D_p$ since $\tilde{\Phi}$ and Ψ are two continuous functions within D_p, which can be followed from Sobolev's Inequality (see [15, Lemma 4.3.4] for example) based on the fact that both $\tilde{\Phi}$ and Ψ are in $H^2(D_p)$. Hence, $\Phi(\mathbf{r}_j)$ is well defined by (24).

Next, with (9), we rewrite the integral $\int_{D_s} c_i(\mathbf{r})\Phi(\mathbf{r})d\mathbf{r}$ as

$$\int_{D_s} c_i(\mathbf{r})\Phi(\mathbf{r})d\mathbf{r} = \int_{D_s} c_i(\mathbf{r})\tilde{\Phi}(\mathbf{r})d\mathbf{r} + \int_{D_s} c_i(\mathbf{r})(\Psi(\mathbf{r}) + G(\mathbf{r}))d\mathbf{r}. \tag{26}$$

Applying (24) and the above expression to (8) immediately gives a new expression of the electrostatic free energy term F_{es} in the form

$$F_{es} = \frac{1}{2}\sum_{j=1}^{n_p} Q_j[\tilde{\Phi}(\mathbf{r}_j) + \Psi(\mathbf{r}_j) + \tilde{G}(\mathbf{r}_j)] + \frac{1}{2}\sum_{i=1}^{n} q_i\left[\int_{D_s} c_i\tilde{\Phi}d\mathbf{r} + \int_{D_s} c_i(\Psi + G)d\mathbf{r}\right]. \tag{27}$$

Clearly, by the above expression, the electrostatic free energy term F_{es} can now be calculated without involving any singular difficulty. In fact, to compute F_{es}, we only need to solve a well defined Poisson-like problem (16) for Ψ one time since Ψ is independent of c. We then solve another well defined Poisson-like problem (15) for $\tilde{\Phi}$ for each given c. In this way, we significantly simplify the calculation of F_{es} while overcoming the singular difficulties.

Furthermore, with (23), we reduce $F_{es}(\Phi, c)$ from a double variable function into a single variable function, $F_{es}(\Phi(c), c)$. Since the values of $\Psi(\mathbf{r}_j)$ and $\tilde{G}(\mathbf{r}_j)$ are independent of c, they can be dropped from the expression of (27) without any affection on the solution of the minimization problem.

Combining all the above modifications together, we obtain our new electrostatic free energy functional as defined by

$$f(c) = \frac{1}{2}[f_{es,1}(c) + f_{es,2}(c) + f_{es,3}(c)] + F_{id}(c) + F_G(c), \tag{28}$$

where $F_{id}(c)$ and $F_G(c)$ are given in (7), and $f_{es,i}$ for $i = 1, 2, 3$ are defined by

$$f_{es,1}(c) = \sum_{i=1}^{n} q_i \int_{D_s} \tilde{\Phi}(c)(\mathbf{r})c_i(\mathbf{r})d\mathbf{r}, \qquad f_{es,2}(c) = \sum_{j=1}^{n_p} Q_j\tilde{\Phi}(c)(\mathbf{r}_j), \tag{29}$$

and

$$f_{es,3}(c) = \sum_{i=1}^{n} q_i \int_{D_s} [\Psi(\mathbf{r}) + G(\mathbf{r})]c_i(\mathbf{r})d\mathbf{r}. \tag{30}$$

The remaining question is how to select the minimum search space V. Note that the function $S(x) = x(\ln x - 1)$, which is used in the definition of F_{id}, is undefined at $x = 0$ but can be fixed by setting $S(0) = 0$ since $\lim_{x\to 0^+} S(x) = 0$. Also, because each c_i is an ionic concentration function, it should be bounded on D_s almost everywhere. Hence, we set the search space $V = [V_0]^n$ with

$$V_0 = \{v \in L^2(\Omega) \mid v = 0 \text{ in } D_p, \text{ and } 0 \le v \le M \text{ a.e. } D_s\}, \tag{31}$$

where M is a sufficiently large upper bound, and $[V_0]^n$ denotes the product space $V_0 \times V_0 \times \cdots \times V_0$ (n times). Clearly, V_0 is a closed and bounded convex subset of the function space $L^2(\Omega)$.

Consequently, we have modified the traditional electrostatic free energy minimization problem (3) as a new modified electrostatic free energy minimization problem as follows:

$$\begin{aligned} &\text{Find } c^* \in V \text{ such that} \\ &f(c^*) = \min\{f(c) \mid c \in V\}, \end{aligned} \tag{32}$$

where $f : V \subset [L^2(\Omega)]^n \to \mathbb{R}$ is given in (28), and V is the domain of f.

5. Analysis on our new modified minimization problem

In this section, we present an analysis on our new modified electrostatic free energy minimization problem (32), and discuss its relationship with PBE.

We start with the calculation of the first and second Fréchet differentials $f'(c)v$ and $f''(c)(v, w)$ of f at each interior point c of V. Here $f'(c)$ and $f''(c)$ are continuous linear and bilinear functionals on $[L^2(\Omega)]^n$ and $[L^2(\Omega)]^n \times [L^2(\Omega)]^n$, respectively, which are defined by

$$f'(c)v = \sum_{i=1}^{n} \frac{\partial f(c)}{\partial c_i} v_i, \quad \text{and} \quad f''(c)(v, w) = \sum_{i,j=1}^{n} \frac{\partial^2 f(c)}{\partial c_j \partial c_i}(v_i, w_j), \tag{33}$$

where $v, w \in [L^2(\Omega)]^n$ with $v = (v_1, v_2, \ldots, v_n)$ and $w = (w_1, w_2, \ldots, w_n)$, and the partial derivatives $\frac{\partial f(c)}{\partial c_i}$ and $\frac{\partial^2 f(c)}{\partial c_j \partial c_i}$ are continuous linear and bilinear functionals on $L^2(\Omega)$ and $L^2(\Omega) \times L^2(\Omega)$, respectively [20, Page 309]. In the sense of Gâteaux differential, the first and second partial derivatives of f can be calculated by the following formulas:

$$\frac{\partial f(c)}{\partial c_i} v_i = \left.\frac{df(c + t v_i \mathbf{e}_i)}{dt}\right|_{t=0} \quad \text{and} \quad \frac{\partial^2 f(c)}{\partial c_j \partial c_i}(v_i, w_j) = \left.\frac{\partial^2 f(c + t v_i \mathbf{e}_i + \tau w_j \mathbf{e}_j)}{\partial \tau \partial t}\right|_{t=\tau=0}, \tag{34}$$

where $\mathbf{e}_i$ denotes the unit vector with one for its ith entry and zero for others. Since c is an interior point of V, for any v_i and w_j in $L^2(\Omega)$, the points $c + t v_i \mathbf{e}_i$ and $c + t v_i \mathbf{e}_i + \tau w_j \mathbf{e}_j$ are in V for sufficiently small t and τ, making the expressions of (34) well defined.

All the terms of $f(c)$ can be calculated for their first and second partial derivatives via (34) except $f_{es,2}(c)$, since $f_{es,2}(c)$ is a singular distribution. To find the partial derivatives of $f_{es,2}(c)$, we need the following lemma.

Lemma 5.1. *Let $\delta_{\mathbf{r}_0}$ be the Dirac delta distribution at $\mathbf{r}_0 \in D_p$. If $\tilde{\Phi}(c)$ is defined in (23), then $\delta_{\mathbf{r}_0}(\tilde{\Phi}(c)) = \tilde{\Phi}(c)(\mathbf{r}_0)$, and its partial derivative $\frac{\partial \delta_{\mathbf{r}_0}(\tilde{\Phi}(c))}{\partial c_i}$ is given by*

$$\frac{\partial \delta_{\mathbf{r}_0}(\tilde{\Phi}(c))}{\partial c_i} = 4\pi q_i L^{-1} \delta_{\mathbf{r}_0} \quad \text{for } i = 1, 2, \ldots, n, \tag{35}$$

Proof. It is known that there exists a sequence of regular distributions, $\{\delta^n_{\mathbf{r}_0}\}$, such that $\delta^n_{\mathbf{r}_0}$ converges to $\delta_{\mathbf{r}_0}$ in the following sense

$$\lim_{n\to\infty} \delta^n_{\mathbf{r}_0}(v) = \delta_{\mathbf{r}_0}(v) \quad \forall v \in \mathcal{D}(\mathbb{R}^3),$$

where $\mathcal{D}(\mathbb{R}^3)$ denotes the test function space [12]. Several constructions of sequences $\delta^n_{\mathbf{r}_0}$ are available (see [21, section 6] and Example 6.2.18 in [16]). Here we follow Example 6.2.18 in [16] to construct $\delta^n_{\mathbf{r}_0}$ by

$$\delta^n_{\mathbf{r}_0}(v) = \int_{\mathbb{R}^3} f_n(\mathbf{r} - \mathbf{r}_0) v(\mathbf{r}) d\mathbf{r} \quad \text{for } n = 1, 2, 3, \ldots, \tag{36}$$

where $f_n(\mathbf{r})$ is given by

$$f_n(\mathbf{r}) = \alpha_n / [(1 + n^2 x^2)(1 + n^2 y^2)(1 + n^2 z^2)],$$

where $\alpha_n = (n/\pi)^3$, and $\mathbf{r} = (x, y, z)$.

Similar to the proof of Example 6.2.18 in [16], it can be shown that

$$\delta^n_{\mathbf{r}_0}(\tilde{\Phi}(c)) = \int_\Omega f_n(\mathbf{r} - \mathbf{r}_0) \tilde{\Phi}(c)(\mathbf{r}) d\mathbf{r} \to \delta_{\mathbf{r}_0}(\tilde{\Phi}(c)) \quad \text{as } n \to \infty.$$

By (23), it is easy to get

$$\frac{\partial \tilde{\Phi}(c)}{\partial c_i} = 4\pi q_i L^{-1}. \tag{37}$$

Thus, the partial derivatives of $\delta^n_{\mathbf{r}_0}(\tilde{\Phi}(c))$ can be calculated by (34) as follows

$$\begin{aligned}
\frac{\partial \delta^n_{\mathbf{r}_0}(\tilde{\Phi}(c))}{\partial c_i} v_i &= \left.\frac{d}{dt} \int_\Omega f_n(\mathbf{r} - \mathbf{r}_0) \tilde{\Phi}(c + t v_i \mathbf{e}_i)(\mathbf{r}) d\mathbf{r}\right|_{t=0} \\
&= \int_\Omega f_n(\mathbf{r} - \mathbf{r}_0) \frac{\partial \tilde{\Phi}(c)}{\partial c_i} v_i(\mathbf{r}) d\mathbf{r} \\
&= \int_\Omega f_n(\mathbf{r} - \mathbf{r}_0) 4\pi q_i L^{-1} v_i(\mathbf{r}) d\mathbf{r} = 4\pi q_i \delta^n_{\mathbf{r}_0}(L^{-1} v_i).
\end{aligned}$$

Letting $n \to \infty$ on the both sides of the above expression immediately gives

$$\frac{\partial \delta_{\mathbf{r}_0}(\tilde{\Phi}(c))}{\partial c_i} v_i = 4\pi q_i \delta_{\mathbf{r}_0}(L^{-1} v_i) \quad v_i \in V_0. \tag{38}$$

Furthermore, since L^{-1} is self-adjoint, we have

$$\delta_{\mathbf{r}_0}(L^{-1} v_i) = \langle \delta_{\mathbf{r}_0}, L^{-1} v_i \rangle = \langle L^{-1} \delta_{\mathbf{r}_0}, v_i \rangle = L^{-1} \delta_{\mathbf{r}_0}(v_i).$$

Applying the above identity to (38) implies (35).

We now present the first and second derivatives of f in Lemma 5.2.

Lemma 5.2. *Let f be a functional given in (28) with domain V. The first and second derivatives of f at each interior point c of V can be found as follows:*

$$f'(c)v = \sum_{i=1}^{n} \int_{D_s} \left[q_i \Phi(\mathbf{r}) + \frac{1}{\beta} \ln(c_i(\mathbf{r}) \Lambda_i^3) - \mu_i \right] v_i(\mathbf{r}) d\mathbf{r} \quad \forall v \in [L^2(\Omega)]^n, \tag{39}$$

and for any $v, w \in [L^2(\Omega)]^n$,

$$f''(c)(v, w) = 4\pi \sum_{i,j=1}^{n} q_i q_j \int_{D_s} L^{-1} v_i(\mathbf{r}) w_j(\mathbf{r}) d\mathbf{r} + \frac{1}{\beta} \sum_{i=1}^{n} \int_{D_s} \frac{1}{c_i} v_i w_i d\mathbf{r}. \tag{40}$$

Proof. By (34), it is easy to get

$$\begin{aligned} &\frac{\partial F_{id}(c)}{\partial c_i} = \frac{1}{\beta} \ln(c_i \Lambda_i^3), \qquad \frac{\partial^2 F_{id}(c)}{\partial c_j \partial c_i} = \begin{cases} \dfrac{1}{\beta c_i} & j = i, \\ 0 & j \neq i, \end{cases} \qquad \frac{\partial F_G(c)}{\partial c_i} = -\mu_i, \\ &\frac{\partial^2 F_G(c)}{\partial c_j \partial c_i} = 0, \qquad \frac{\partial f_{es,3}(c)}{\partial c_i} = q_i(\Psi + G), \qquad \frac{\partial^2 f_{es,3}(c)}{\partial c_j \partial c_i} = 0. \end{aligned} \tag{41}$$

By (37), the partial derivative $\frac{\partial f_{es,1}}{\partial c_i}$ can be calculated as follows:

$$\begin{aligned} \frac{\partial f_{es,1}(c)}{\partial c_i} v_i &= \frac{d}{dt} \int_{D_s} \tilde{\Phi}(c + t v_i \mathbf{e}_i) \left(q_i(c_i + t v_i) + \sum_{j=1, j\neq i}^{n} q_j c_j \right) d\mathbf{r} \Big|_{t=0} \\ &= \int_{D_s} \left(\frac{\partial \tilde{\Phi}(c)}{\partial c_i} v_i \sum_{j=1}^{n} q_j c_j + \tilde{\Phi}(c) q_i v_i \right) d\mathbf{r} \\ &= \int_{D_s} \left(4\pi q_i L^{-1} \sum_{j=1}^{n} q_j c_j + q_i \tilde{\Phi}(c) \right) v_i d\mathbf{r} \\ &= \int_{D_s} \left(q_i \tilde{\Phi}(c) + q_i \tilde{\Phi}(c) \right) v_i d\mathbf{r} = \int_{D_s} 2 q_i \tilde{\Phi}(c) v_i d\mathbf{r} \quad \forall v_i \in V_0, \end{aligned}$$

from which it implies

$$\frac{\partial f_{es,1}(c)}{\partial c_i} = 2 q_i \tilde{\Phi}(c) \quad \text{for } i = 1, 2, \ldots, n. \tag{42}$$

With (34) and (37), we then find

$$\frac{\partial^2 f_{es,1}(c)}{\partial c_j \partial c_i} = 2 q_i \frac{\partial \tilde{\Phi}(c)}{\partial c_j} = 8\pi q_i q_j L^{-1}. \tag{43}$$

Using (35), we can easily obtain

$$\begin{aligned} \frac{\partial f_{es,2}(c)}{\partial c_i} &= \frac{\partial}{\partial c_i} \left[\sum_{j=1}^{n_p} Q_j \delta_{\mathbf{r}_j}(\tilde{\Phi}(c)) \right] = \sum_{j=1}^{n_p} Q_j \frac{\partial \delta_{\mathbf{r}_j}(\tilde{\Phi}(c))}{\partial c_i} \\ &= \sum_{j=1}^{n_p} 4\pi Q_j q_i L^{-1} \delta_{\mathbf{r}_j} = q_i 4\pi L^{-1} \sum_{j=1}^{n_p} Q_j \delta_{\mathbf{r}_j} = q_i u \quad \text{for } i = 1, 2, \ldots, n, \end{aligned} \tag{44}$$

where $u = 4\pi L^{-1} \sum_{j=1}^{n_p} Q_j \delta_{\mathbf{r}_j}$. It can be easily seen that

$$u = G + \Psi,$$

which is the solution of the Poisson dielectric model in the case of pure water solvent (i.e., all $c_i = 0$). Since u is independent of c, it is clear that

$$\frac{\partial^2 f_{es,2}(c)}{\partial c_j \partial c_i} = 0 \quad \text{for } i, j = 1, 2, \ldots, n. \tag{45}$$

By (41) to (45), the partial derivatives of f are found as follows:

$$\frac{\partial f(c)}{\partial c_i} = q_i\Phi + \frac{1}{\beta}\ln(c_i\Lambda_i^3) - \mu_i, \qquad \frac{\partial^2 f(c)}{\partial c_j \partial c_i} = \begin{cases} 4\pi q_i^2 L^{-1} + \dfrac{1}{\beta c_i}, & j = i, \\ 4\pi q_i q_j L^{-1}, & j \neq i, \end{cases} \tag{46}$$

from which we obtain the first and second derivatives of f as given in (39) and (40). This completes the proof of Lemma 5.2.

We now present the main results of our analysis on the minimization problem (32) in the following theorem.

Theorem 5.3. *Let f be a functional given in (28) with V being its domain defined in (31), and $f'(c)$ be the derivative of f given in (39). Then, the minimization problem (32) has a unique minimum on V. Moreover, the unique minimizer is also a local minimizer of f, and satisfies the Euler equation:*

$$f'(c) = 0. \tag{47}$$

Proof. Since L^{-1} is strictly positive, for any nonzero $v \in [L^2(\Omega)]^n$, we get

$$\begin{aligned} f''(c)(v, v) &= 4\pi \left\langle L^{-1}\sum_{i=1}^n q_i v_i, \sum_{i=1}^n q_i v_i \right\rangle_{L^2(\Omega)} + \frac{1}{\beta}\sum_{i=1}^n \int_{D_s} \frac{1}{c_i}(v_i(\mathbf{r}))^2 d\mathbf{r} \\ &\geq 4\pi \left\langle L^{-1}\sum_{i=1}^n q_i v_i, \sum_{i=1}^n q_i v_i \right\rangle_{L^2(\Omega)} > 0, \end{aligned} \tag{48}$$

showing that $f''(c)$ is strictly positive on $[L^2(\Omega)]^n$. Thus, f is strictly convex on V according to [22, Corollary 42.8, Page 248].

From the expressions (28), (39) and (40) it can be seen that f is continuous on V while f' and f'' are continuous at each interior point of V. Thus, f is lower semicontinuous on V. Hence, from [22, Proposition 38.7, Page 150] it can be known that f is weak sequentially lower semicontinuous on V.

We next prove the solution existence of (32). Let $\{v_k\}$ be a minimum sequence of V satisfying that

$$\lim_{k\to\infty} f(v_k) = \min_{v\in V} f(v).$$

Since $V = [V_0]^n$ with V_0 being a closed convex and bounded subset of a reflexive function space $L^2(\Omega)$, there exists a subsequence, $\{v_{k_j}\}$, of $\{v_k\}$ such that it converges weakly to a point c^* of V in the following sense:

$$\lim_{j\to\infty} l(v_{k_j,i}) = l(c_i^*), \quad i = 1, 2, \ldots, n,$$

where $v_{k_j,i}$ and c_i^* denote the ith components of v_{k_j} and c^*, respectively, and l denotes any bounded linear functional on $L^2(\Omega)$. Hence, the fact that f is weak sequentially lower semicontinuous on V gives

$$\liminf_{j\to\infty} f(v_{k_j}) \geq f(c^*),$$

from which it implies that c^* is a minimizer of f on V: $f(c^*) = \min_{v\in V} f(v)$.

The solution uniqueness is proved as follows. Suppose that f has another different minimizer $c' \in V$. Since V is convex and f is strictly convex, clearly, $(c^* + c')/2 \in V$ and

$$f((c^* + c')/2) < \frac{1}{2}[f(c^*) + f(c')] = \min_{v\in V} f(v),$$

which is a contradiction. This proves that f has a unique minimum on V.

Furthermore, we show that c^* is a local minimizer of f. Let d be a local minimizer of f. That is, there exists a sufficiently small $\eta > 0$ such that

$$f(d) \leq f(v) \quad \forall v \in B(d; \eta) \subset V,$$

where $B(d; \eta) = \{v \mid \|v - d\| < \eta\}$. Clearly, for any $w \in V$ with $w \neq d$, there exists $t \in (0, 1)$ such that $d + t(w - d) \in B(d; \eta)$. Thus,

$$f(d) \leq f(d + t(w - d)),$$

and the convexity of f on V gives

$$f(d + t(w - d)) = f((1 - t)d + tw) \leq (1 - t)f(d) + tf(w).$$

Hence, from the above two inequalities we can get

$$f(d) \le f(w) \quad \forall w \in V,$$

showing that d is a minimizer of f on V. By the minimum uniqueness, we claim $d = c^*$. This proves that c^* is a local minimizer. Hence, from [22, Theorem 40.B, Page 194] it follows that c^* is a solution of the Euler equation. This completes the proof of Theorem 5.3.

Corollary 5.4. *The PBE model is a reduced form of the Euler equation (47), and the following three assertions are equivalent:*

1. *The PBE model (1) has a unique solution.*
2. *The Euler equation (47) has a unique solution.*
3. *The minimization problem (32) has a unique solution.*

Proof. Clearly, the Euler equation (47) can be written as a system of $n+1$ equations − the first equation is the Poisson dielectric model (4), and the other n equations are given by

$$q_i\Phi + \frac{1}{\beta}\ln(c_i\Lambda_i^3) - \mu_i = 0 \quad \text{for } i = 1, 2, \ldots, n. \tag{49}$$

The above equations can then be simplified as

$$c_i(\mathbf{r}) = M_i e^{-\beta q_i \Phi(\mathbf{r})} \quad \text{with } M_i = \Lambda_i^{-3} e^{\beta\mu_i},\ \mathbf{r} \in D_s,\ i = 1, 2, \ldots, n. \tag{50}$$

Applying the above expressions to the Poisson dielectric model (4) immediately yields the PBE model (1). This proves that the PBE model is a reduced form of the Euler equation. Hence, it is obvious that the solution existence and uniqueness of PBE is equivalent to that of the Euler equation.

If the Euler equation (47) has a solution c^*, we then can use [22, Theorem 40.B, Page 194] to claim that c^* is a local minimizer of f, since the second derivative of f has been known to exist and to be positive and continuous at each interior point of V. The remaining parts of the proof can be found in the proof of Theorem 5.3. This completes the proof of the corollary.

Because of Corollary 5.4, the existence of a local minimizer of f can be followed from the solution existence of PBE, which has been done in the literature [23,10,24]. This assertion offers a justification to the local minimizer d of f used in the proof of Theorem 5.3.

Since PBE is a reduced form of the Euler equation (47), its theoretical analysis and numerical solution can be more easily done than the case of the minimization problem (32). The optimal solution c^* of the electrostatic free energy minimization problem can be found by using (50) when a PBE solution Φ is given. This partially explains why it is PBE, instead of an electrostatic free energy minimization problem, that has been often theoretically analyzed and numerically solved in the fields of mathematical biology, computational biochemistry, and bioengineering [25,26,11,27–29].

Clearly, applying (50) to the solution decomposition (9) leads to a solution decomposition for the PBE model in the form

$$\Phi(\mathbf{r}) = \tilde{\Phi}^*(\mathbf{r}) + \Psi(\mathbf{r}) + G(\mathbf{r}), \quad \mathbf{r} \in \Omega, \tag{51}$$

where G and Ψ are the same as the ones in (9), and $\tilde{\Phi}^*$ denotes the solution of the nonlinear elliptic interface problem

$$\begin{cases} -\Delta\tilde{\Phi}(\mathbf{r}) = 0, & \mathbf{r} \in D_p, \\ -\epsilon_s\Delta\tilde{\Phi}(\mathbf{r}) - 4\pi\displaystyle\sum_{i=1}^{n} q_i g_i(\mathbf{r}) e^{-\beta q_i\tilde{\Phi}(\mathbf{r})} = 0, & \mathbf{r} \in D_s, \\ \tilde{\Phi}(\mathbf{s}^+) = \tilde{\Phi}(\mathbf{s}^-), \quad \varepsilon_s\dfrac{\partial\tilde{\Phi}(\mathbf{s}^+)}{\partial\mathbf{n}(\mathbf{s})} = \varepsilon_p\dfrac{\partial\tilde{\Phi}(\mathbf{s}^-)}{\partial\mathbf{n}(\mathbf{s})}, & \mathbf{s} \in \Gamma, \\ \tilde{\Phi}(\mathbf{r}) \to 0 & \text{as } |\mathbf{r}| \to \infty, \end{cases} \tag{52}$$

where $g_i(\mathbf{r}) = M_i e^{-\beta q_i(\Psi(\mathbf{r})+G(\mathbf{r}))}$. This PBE solution decomposition can be valuable in the theoretical and numerical study of PBE. It has been used to construct a new PBE analysis and a new fast PBE finite element solver in [24]. We note that there exist other PBE solution decomposition methods as given in [23,30–32]. In the decomposition from [30], Φ was split within D_p only. In the decompositions from [23,31,32], elliptic boundary value problems with discontinuous coefficients were used to describe Ψ and $\tilde{\Phi}$, which had definitions only in the weak sense. In addition, these solution decompositions were made only for a symmetric 1:1 ionic solvent (i.e., the case of $n = 2$, $q_1 = 1$, and $q_2 = -1$) such as the salt solution containing sodium (Na^+) and chloride (Cl^-) ions.

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