

An Inverse Averaging Finite Element Method for Solving the Size-Modified Poisson-Nernst-Planck Equations in Ion Channel Simulations

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Abstract. In this work, an inverse averaging finite element method (IAFEM) is developed for solving the size-modified Poisson-Nernst-Planck (SMPNP) equations. Comparing with the classical Poisson-Nernst-Planck (PNP) equations, the SMPNP equations add a nonlinear term to each of the Nernst-Planck (NP) fluxes to describe the steric repulsion which can treat multiple nonuniform particle sizes in simulations. Since the new terms include sums and gradients of ion concentrations, the nonlinear coupling of SMPNP equations is much stronger than that of PNP equations. By introducing a generalized Slotboom transform, each of the size-modified NP equation is transformed into a self-adjoint equation with exponentially behaved coefficient, which has similar simple form to the standard NP equation with the Slotboom transformation. This treatment enables employing our recently developed inverse averaging technique to deal with the exponential coefficients of the reformulated formulations, featured with advantages of numerical stability and flux conservation especially in strong nonlinear and convection-dominated cases. Comparing with previous stabilization methods, the IAFEM developed in this paper can still possess the numerical stability when dealing with convection-dominated problems. And it is more concise and easier to be numerically implemented. Numerical experiments about a model problem with analytic solutions are presented to verify the accuracy and order of IAFEM for SMPNP equations. Studies about the size-effects of a sphere model and an ion channel

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system are presented to show that our IAFEM is more effective and robust than the traditional finite element method (FEM) when solving SMPNP equations in simulations of biological systems.

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1 Introduction

“The effects of finite particle size on electrostatics, density profiles, and diffusion have been a long-existing topic in the study of ionic solution.” [30] As a continuous electrodiffusion model, the classical Poisson-Nernst-Planck (PNP) equations play an important role in the electrodiffusion reaction process and have been widely used to describe the electrodiffusion of ions and charge transport in applications including the solvated biomolecular system [29, 31], semiconductors [21, 33, 37], electrochemical systems [4, 10, 32] and ion channels [7, 11, 39]. Although the PNP equations have achieved a lot of success in various applications, it still has some limitations due to the neglected steric effects of ions in its mean-field derivation, for example, the PNP model leads to unphysical crowding of ions near charged surfaces and incorrect dynamics of ion transport, and the difference between two cations with the same charge cannot be distinguished when simulating the concentration distribution of ions. To incorporate the effects of finite particle sizes in the study of ionic solutions, many improvements are made through introducing exclusion terms from the liquid-state theory or the density functional theory (DFT), e.g. see [15, 16, 34, 36] and references therein. In addition, based on the framework of the PNP model, several versions of the modified PNP theory have been developed in the literature to account for steric effects [20, 22, 23, 25, 35, 38]. Among these theories, the Borukhov model [5] attracts people’s attention because it captures basic size effects only with a simplified model. The Borukhov model modifies the free energy functional of the ionic system (mean-field approximation) by adding an ideal-gas-like solvent entropy term, which represents the unfavorable energy used to model the over-packing or crowding of the ions and solvent molecules. Thus the steric effects are taken into account in the model. Lu and Zhou by generalizing the Borukhov model get a class of size-modified Poisson-Nernst-Planck (SMPNP) equations via the inclusion of the entropy of solvent molecules in the electrostatic free-energy functional [30]. Different from many other works, the SMPNP model is able to treat multiple nonuniform particle sizes in simulations.

Comparing with the classical PNP equations [29], the SMPNP model adds a nonlinear term to each of Nernst-Planck (NP) equations aiming at describing the steric repulsion (see Eq. (2.2)). Since the new term includes sums and gradients of ion concentrations,

the nonlinear coupling of SMPNP equations is much stronger than that of PNP equations. This brings many difficulties for solving SMPNP equations. The NP equations are typical convection-diffusion equations. And the convection dominance will lead to numerical oscillations (e.g. negative ion concentration values). Many stabilization schemes are proposed to avoid non-physical numerical oscillations, e.g. see [8, 43, 45]. Tu et al. [43] employed the streamline upwind/Petrov-Galerkin (SUPG) method and the Pseudo Residual-Free Bubble function (PRFB) scheme to enhance the numerical robustness and convergence of the finite element scheme. However, for some macro-molecular systems, e.g., the KcsA ion channel, the SUPG method cannot eliminate all non-physical numerical oscillations or produce convergent numerical solutions [45]. By combining the “upwind” characteristic of the SUPG method and the polishing effect of the interior penalty (IP) method [6, 13], Wang et al. [45] proposed a SUPG-IP method to solve PNP equations, which performs better in preserving numerical solution positivity and is much more robust than the standard FEM and the SUPG method when simulating KcsA ion channels. For modified PNP equations with steric effect, based on the “SUPG” framework, a fast stabilized finite element method is proposed for solving the modified PNP equations with uniform particle sizes [8]. However, in the above stabilization schemes, derivations of stabilization terms need a lot of complex interface jump integral calculations, which increases the complexity of their numerical implementations, especially with irregular geometric biological channels. In addition, selecting appropriate stabilization parameters is skillful for different macro-molecule systems. Large stabilization parameters are helpful to numerical convergence, but they will affect numerical accuracy. In addition, the stabilized methods generally have no flux conservation properties.

Especially, we noticed that the modified PNP equations with ionic steric effects (SPNP) were studied by finite difference methods based on harmonic-mean approximations to the exponential coefficients of the reformulated NP equations in [12]. The difference from [12] is that the exponential coefficients are approximated based on the inverse averaging of the integral on the element instead of directly on the entire grid node in this paper. Although the finite difference method has been widely used to solve the PNP equations, e.g. see [14, 18, 26] and references therein, the implementation and accuracy of the numerical solution are not so good when it is applied to simulate the actual biomolecular systems with highly irregular surfaces, such as cell membrane, DNA and ion channels. The Finite element method (FEM) has more flexibility and adaptability in irregular regions, which has shown great advantages in solving PNP and modified PNP equations in many actual biomolecular simulations [27, 29, 30, 41, 46]

Inspired by [48], we apply the inverse averaging finite element method (IAFEM) for solving SMPNP equations and derive an effective and robust numerical scheme for biomolecular system simulations with the SMPNP model. In this work, we notice that distributions of ion concentrations cannot be approximated with piecewise polynomials directly, but the size-modified flux densities vary moderately in biological channels. Thus we treat each of the size-modified flux densities as a whole by introducing a set of generalized Slotboom variables, which eliminate cross-terms in the size-modified NP (SMNP)

equations. Then SMNP equations are transformed into self-adjoint second-order elliptic equations with exponentially behaved coefficients. In order to deal with these exponential coefficients, we employ an inverse averaging technique introduced in [48]. The main idea is to use the exponential coefficients' harmonic averages to approximate them on every tetrahedral element. And their harmonic averages are calculated on each edge of the tetrahedral element with an inverse averaging technique. This strategy is reasonable because it takes advantage of the moderate variations of size-modified flux densities.

The rest of the paper is organized as follows. In Section 2, the mathematical model and relevant governing equations are introduced. The singular decomposition of permanent charges for Poisson equations and the reformulation of SMNP equations with the help of generalized Slotboom variables are also presented in this section. In Section 3, the IAFEM is introduced to discretize the SMNP equations. Numerical experiments about a model problem with analytic solutions are presented to verify the accuracy and order of the IAFEM for SMPNP equations. And studies about the size-effects of a sphere model and the an ion channel system are also reported in Section 4. This paper is ended with Section 5.

2 The mathematical model

In this section we briefly overview the problem and review the relevant equations.

2.1 Governing equations

Let $\Omega \subset \mathbb{R}^d$ ($d=2,3$) be an open domain. In this work, we consider the SMPNP equations [30] by coupling the SMNP equations

$$\frac{\partial c_i}{\partial t} = -\nabla \cdot J_i, \quad i=1,2,\dots,K, \quad \text{in } \Omega_s, \quad (2.1)$$

$$J_i = -D_i \left(\nabla c_i + \beta q_i c_i \nabla \phi + \frac{k_i c_i}{1 - \sum_l a_l^3 c_l} \sum_l a_l^3 \nabla c_l \right), \quad (2.2)$$

and the Poisson equation with the internal interface $\Gamma_m = \bar{\Omega}_s \cap \bar{\Omega}_m$:

$$-\nabla \cdot (\epsilon \nabla \phi) = \rho^f + \lambda \sum_{i=1}^K q_i c_i, \quad \text{in } \Omega = \Omega_s \cup \Omega_m, \quad (2.3)$$

$$\phi_m = \phi_s, \quad \epsilon_m \frac{\partial \phi_m}{\partial \vec{n}} = \epsilon_s \frac{\partial \phi_s}{\partial \vec{n}}, \quad x \in \Gamma_m, \quad (2.4)$$

where $c_i(x,t)$ is the concentration of the i th ion species carrying charge $q_i = z_i e_c$, z_i is the valence of the i th ion species, and e_c is the elementary charge. J_i is the size-modified flux density, in which D_i is a spatial-dependent diffusion coefficient, and ϕ is the electrostatic potential, K is the number of diffusive ion species considered in the solution system.

The constant $\beta = 1/(k_B T)$ is the inverse Boltzmann energy, where k_B is the Boltzmann constant, and T is the absolute temperature. ϵ is the piecewise dielectric constant with $\epsilon = \epsilon_m \epsilon_0$ in Ω_m and $\epsilon = \epsilon_s \epsilon_0$ in Ω_s , where ϵ_0 is the dielectric constant of vacuum, and the typical values of ϵ_m and ϵ_s are 2 and 80, respectively. The characteristic function λ is the indicator function of Ω_s , that is

$$\lambda = \begin{cases} 0, & \text{in } \Omega_m, \\ 1, & \text{in } \Omega_s, \end{cases}$$

which suggests that mobile ions only exist in the solvent region. The permanent (fixed) charge distribution

$$\rho^f(x) = \sum_j q_j \delta(x - x_j),$$

which is a sum of singular charges q_j located at x_j inside the biomolecule, and δ is the Dirac-delta function. The constant $k_i = a_i^3/a_0^3$, where a_i is the effective size of the i th ion species, and a_0 is the solvent molecule size. The size a_i can be arbitrary, and does not need to be larger than the solvent molecule size a_0 .

Comparing with the classical PNP equations (cf. [29]), the SMPNP equations add non-linear terms $\frac{k_i c_i}{1 - \sum_l a_l^3 c_l} \sum_l a_l^3 \nabla c_l$ ($l = 1, 2, \dots, K$), to flux densities in (2.2) to describe the steric repulsion. If size-effects are not considered, that is, $k_i = 0$ (or $a_i = 0$), SMNP equations (2.1) directly reduce to classical NP equations as follows

$$\frac{\partial c_i}{\partial t} = \nabla \cdot D_i (\nabla c_i + \beta q_i c_i \nabla \phi), \quad i = 1, 2, \dots, K, \text{ in } \Omega_s. \tag{2.5}$$

For brevity, we write the NP equations and SMNP equations as

$$\begin{aligned} \frac{\partial c_i}{\partial t} &= -\nabla \cdot J_i, \quad \text{in } \Omega_s, \quad i = 1, 2, \dots, K, \\ J_i &= -D_i (\nabla c_i + \beta q_i c_i \nabla \phi + \mathbf{N}_{k_i}(c_i)), \end{aligned} \tag{2.6}$$

where

$$\mathbf{N}_{k_i}(c_i) = k_i \frac{c_i}{1 - \sum_l a_l^3 c_l} \sum_l a_l^3 \nabla c_l, \quad k_i \begin{cases} = 0, & \text{for NP equations,} \\ \neq 0, & \text{for SMNP equations.} \end{cases} \tag{2.7}$$

2.2 Boundary conditions

In this work, including the internal interface conditions (2.4) for the Poisson equation (2.3), we consider the following boundary conditions

$$\begin{cases} [\phi] = 0, & [\epsilon \frac{\partial \phi}{\partial \vec{n}}] = 0, & \text{on } \Gamma_m, \\ \phi = \phi_0, & & \text{on } \Gamma_s, \\ c_i = c_i^\infty, & & \text{on } \Gamma_s \\ J_i \cdot \vec{n} = 0, & & \text{on } \Gamma_m, \end{cases} \tag{2.8}$$

In fact, $\phi^s(x)$ can be given analytically by the sum of Coulomb potentials, that is

$$\phi^s(x) = \sum_{j=1}^N \frac{q_j}{\epsilon_m 4\pi |x - x_j|},$$

where N is the total number of particles in the biomolecule, and $|x - x_j|$ denotes the distance between the current position x and the particle center x_j .

The harmonic component ϕ^h is the solution of a Laplace equation:

$$\begin{aligned} -\Delta\phi^h(x) &= 0, & x \in \Omega_m, \\ \phi^h(x) &= -\phi^s(x), & x \in \Gamma_m. \end{aligned} \quad (2.10)$$

Subtracting the above two components ϕ^s and ϕ^h from Eq. (2.3), we get the governing equation of the regular component $\phi^r(x)$:

$$-\nabla \cdot (\epsilon \nabla \phi^r(x, t)) = \lambda \sum_i q_i c_i(x, t), \quad x \in \Omega, \quad (2.11)$$

and the interface conditions

$$\phi_s^r - \phi_m^r = 0, \quad \epsilon_s \frac{\partial \phi_s^r}{\partial n} - \epsilon_m \frac{\partial \phi_m^r}{\partial n} = \epsilon_m \frac{\partial (\phi^s + \phi^h)}{\partial n}, \quad x \in \Gamma_m.$$

It is worth noting that there is no decomposition of the electrostatic potential in the solvent region, thus $\phi(x) = \phi^r(x)$ in Ω_s . Hence, the final regularized SMPNP/PNP equations consist of the regularized Poisson equation (2.11) and the SMNP/NP equations

$$-\nabla \cdot \left(D_i(x) (\nabla c_i(x) + \beta q_i c_i(x) \nabla \phi^r(x)) + \mathbf{N}_{k_i}(c_i(x)) \right) = 0, \quad x \in \Omega_s. \quad (2.12)$$

In the following content, we still also use ϕ to represent the regular component $\phi^r(x)$, and the singular and harmonic components have been considered to get the complete electrostatic potential inside molecules.

Compared to the original model (2.1)-(2.4), the above decompositions (see (2.9)-(2.11)) have a number of nice properties. Firstly, the decomposition of the electrostatic potential only occurs inside biomolecules, so the numerical solution of ϕ^r in Ω_s does not possess the numerical instability problem [19]. Secondly, the singular and harmonic components only need to be solved one time in advance when decoupling the regularized SMPNP/PNP equations. More comments and relative comparisons can be found in [29] and the references therein.

2.4 A transformed form of the SMPNP equations

By introducing a set of generalized Slotboom variables [30], the regularized SMPNP equations (2.11)-(2.12) can be written as

$$-\nabla \cdot (\bar{D}_i \nabla \bar{C}_i) = 0, \quad (2.13)$$

$$-\nabla \cdot (\epsilon \nabla \phi) - \lambda \sum_i^K q_i \bar{C}_i e^{-\Psi_i} = 0, \quad (2.14)$$

with

$$\begin{cases} \Psi_i = \beta q_i \phi - k_i \ln \left(1 - \sum_l^K a_l^3 c_l \right), & k_i = a_i^3 / a_0^3, \\ \bar{D}_i = D_i e^{-\Psi_i}, \\ \bar{C}_i = c_i e^{\Psi_i}. \end{cases} \quad (2.15)$$

Physically, Ψ_i can be seen as a modification of the electrostatic potential ϕ due to the size effects. If the size effect is not considered ($k_i = 0$ or $a_i = 0$), the transformed forms (2.13)-(2.15) reduce to the classical Slotboom transform of PNP equations [29, 40, 42].

The transformed SMNP equation (2.13) is a self-adjoint second-order elliptic equation about the Slotboom variable \bar{C}_i . Different from the classical NP equations, the coefficient \bar{D}_i depends on ϕ and c_i in SMNP equations. Therefore, a semi-implicit scheme is employed in our scheme. In the iterative process of equations decoupling, we use the solution at the $(n-1)$ th step c_i^{n-1} to calculate the coefficient \bar{D}_i , and then solve the transformed Eq. (2.13) to obtain the solution at the current n th step c_i^n . This strategy can make the stiffness matrices symmetric for the generalized Slotboom variable \bar{C}_i . And the condition number of the stiffness matrix derived from discretizing the transformed Eq. (2.13) may be smaller than that of the stiffness matrix produced by the original Eq. (2.12). Thus the decoupling iterative methods applied to the linear system might converge faster [30]. However, in biomolecular simulations, as shown in [29], the discretization of the transformed Eq. (2.13) always leads to an ill-conditioned stiffness matrix because a strong electrostatic field exists near the molecular surface. In addition, the introduction of Slotboom variables makes the Poisson equation (2.14) become nonlinear for the electrostatic potential ϕ . So a nonlinear iterative scheme, e.g. Newton method, is necessary for solving the nonlinear Poisson equation, which may cost much more CPU time. In practical numerical simulations, our previous experience shows that the Newton method is sensitive to the initial value, especially in macromolecular biological channel simulations, e.g. KcsA K^+ channels, see [27, 45]. In order to avoid multi-level nonlinear iteration and improve the efficiency and robustness of the our method, we use the normal unknown variables when solving SMPNP equations (2.13)-(2.14) in this work.

At first, we use the normal variables c_i to rewrite (2.13)-(2.15) as follows:

$$-\nabla \cdot (D_i e^{-\Psi_i} \nabla (e^{\Psi_i} c_i)) = 0, \quad \text{in } \Omega_s, \tag{2.16}$$

$$-\nabla \cdot (\epsilon \nabla \phi) = \lambda \sum_i^K q_i c_i, \quad \text{in } \Omega, \tag{2.17}$$

with

$$\Psi_i = \beta q_i \phi - k_i \ln \left(1 - \sum_l^K a_l^3 c_l \right), \quad k_i = a_i^3 / a_0^3. \tag{2.18}$$

Let $u = \beta e_c \phi$ to nondimensionalize the electrostatic potential, and $q_i = z_i e_c$. Then Eqs. (2.16)-(2.18) become:

$$-\nabla \cdot (D_i e^{-\Psi_i} \nabla (e^{\Psi_i} c_i)) = 0, \quad \text{in } \Omega_s, \tag{2.19}$$

$$-\nabla \cdot (\epsilon \nabla u) = \beta e_c^2 \lambda \sum_i^K z_i c_i, \quad \text{in } \Omega, \tag{2.20}$$

where

$$\Psi_i = z_i u - k_i \ln \left(1 - \sum_l^K a_l^3 c_l \right), \quad k_i = a_i^3 / a_0^3. \tag{2.21}$$

The corresponding boundary conditions become

$$\begin{cases} [u] = 0, & [\epsilon \frac{\partial u}{\partial \vec{n}}] = \beta e_c \epsilon_m \frac{\partial (\phi^s + \phi^h)}{\partial \vec{n}}, & \text{on } \Gamma_m, \\ u = u_0, & & \text{on } \Gamma_D, \\ c_i = c_i^\infty, & & \text{on } \Gamma_D \\ J_i \cdot \vec{n} = 0, & & \text{on } \Gamma_m, \end{cases} \tag{2.22}$$

where $u_0 = \beta e_c \phi_0$, $J_i = -(D_i e^{-\Psi_i} \nabla (e^{\Psi_i} c_i))$, and ϕ_0, c_i^∞ are the applied potential and bulk concentrations defined by (2.8).

3 Inverse averaging finite element method for SMPNP equations

In this section, we will introduce the IAFEM for the reformulated SMPNP equations (2.19)-(2.22) in detail. In order to facilitate the presentation and understanding of the latter contents, we first report some preliminary notations of the finite element discretiza-

tion. Let $H^1(\Omega)$ be the Sobolev space of weakly differentiable functions. Denoted by

$$\begin{aligned} L^2(\Omega) &\equiv \left\{ w: \Omega \rightarrow \mathbb{R} \mid \int_{\Omega} w^2 dx < \infty \right\}, \\ H^1(\Omega) &\equiv \left\{ w \in L^2(\Omega) \mid \int_{\Omega} |\nabla w|^2 dx < \infty \right\}, \\ H_0^1(\Omega) &\equiv \left\{ w \in H^1(\Omega) \mid w|_{\Gamma_D} = 0 \right\} \end{aligned}$$

be the spaces with associated norms:

$$\|w\|_0 \equiv \left(\int_{\Omega} w^2 dx \right)^{1/2}, \quad |w|_1 \equiv \left(\int_{\Omega} |\nabla w|^2 dx \right)^{1/2}, \quad \|w\|_1^2 \equiv |w|_1^2 + \|w\|_0^2,$$

and $\|w\|_{\infty} \equiv \sup_{x \in \Omega} |w(x)|$, and the inner product $(f, g)_{\Omega} := \int_{\Omega} fg dx$.

3.1 Weak forms and finite element discretization of the reformulated SMPNP equations

Integrating by parts, and noting the interface conditions in (2.22), the weak forms of the reformulations (2.19)-(2.22) are to find $c_i \in H^1(\Omega_s)$ ($1 \leq i \leq K$) and $u \in H^1(\Omega)$ satisfying

$$(D_i e^{-\Psi_i} \nabla(e^{\Psi_i} c_i), \nabla v)_{\Omega_s} = 0, \quad \forall v \in H_0^1(\Omega), \quad (3.1)$$

$$(\epsilon \nabla u, \nabla w)_{\Omega} = \left(\beta e_c^2 \lambda \sum_i^K z_i c_i, w \right)_{\Omega} - \beta e_c \left(\epsilon_m \frac{\partial(\phi^s + \phi^h)}{\partial \bar{n}}, w \right)_{\Gamma_m}, \quad \forall w \in H_0^1(\Omega), \quad (3.2)$$

where Ψ_i is defined by (2.21).

Let $\mathcal{T}_h = \{T\}$ be a triangulation of Ω with (triangular/tetrahedral) elements T , $X_h = \{x_i\}_{i=1}^{N_v}$ be the set of all vertices of \mathcal{T}_h . Let $V_h \subset H_0^1(\Omega)$ be the piecewise linear finite element space, and $H_0^1(\Omega)$ is a Sobolev space of weakly differentiable functions which vanish on the boundary of the domain Ω . Denote the nodal basis function in V_h with φ_i , $i = 1, 2, \dots, N_v$, which is linear on the T and

$$\varphi_i(x_i) = 1, \quad \varphi_i(x_j) = 0, \quad j \neq i. \quad (3.3)$$

For a given $T \in \mathcal{T}_h$, we have

$$\int_T \nabla u_h \cdot \nabla v_h dx = \sum_{i,j} e_{ij}^T u_h(x_i) v_h(x_j), \quad \forall u_h, v_h \in V_h. \quad (3.4)$$

Note that $e_{ij}^T = \int_T \nabla \varphi_j \cdot \nabla \varphi_i dT$ represents some geometric information of the element T , and it holds for linear Lagrangian finite element basis functions that $e_{ii}^T = -\sum_{j \neq i} e_{ij}^T$. Then we can easily transform (3.4) to the following simple but important identity

$$\int_T \nabla u_h \cdot \nabla v_h dx = - \sum_{i,j} e_{ij}^T (u_h(x_i) - u_h(x_j))(v_h(x_i) - v_h(x_j)), \quad \forall u_h, v_h \in V_h. \quad (3.5)$$

Let the test function v_h take the linear Lagrangian basis function φ_i at x_i , we have

$$\int_T \nabla u_h \cdot \nabla \varphi_i dx = - \sum_{x_j \in T} e_{ij}^T (u_h(x_i) - u_h(x_j)). \tag{3.6}$$

The finite element discretization of (3.1)-(3.2) is to find $c_{i,h} \in V_h(\Omega_s)$, $1 \leq i \leq K$, and $u_h \in V_h(\Omega)$, such that

$$(D_i e^{-\Psi_{i,h}} \nabla (e^{\Psi_{i,h}} c_{i,h}), \nabla v_h)_{\Omega_s} = 0, \quad \forall v_h \in V_h, \tag{3.7}$$

$$(\epsilon \nabla u_h, \nabla w_h)_{\Omega} = \left(\beta e_c^2 \lambda \sum_{i=1}^K z_i c_{i,h}, w_h \right)_{\Omega} - \beta e_c \left(\epsilon_m \frac{\partial (\phi^s + \phi^h)}{\partial \vec{n}}, w_h \right)_{\Gamma_m}, \quad \forall w_h \in V_h, \tag{3.8}$$

where

$$\Psi_{i,h} = z_i u_h - k_i \ln \left(1 - \sum_l^K a_l^3 c_{l,h} \right), \quad k_i = a_i^3 / a_0^3. \tag{3.9}$$

In order to show differences between finite element approximations of the reformulated and traditional schemes clearly, we also present the standard finite element scheme for (2.12) as follows:

For each i , $1 \leq i \leq K$, find $c_{i,h} \in V_h(\Omega_s)$ and $u_h \in v_h(\Omega)$, such that

$$\left(D_i \left(\nabla c_{i,h} + z_i c_{i,h} \nabla u_h + \frac{k_i c_{i,h}}{1 - \sum_l^K a_l^3 c_{l,h}} \sum_l^K a_l^3 \nabla c_{l,h} \right), \nabla v_h \right)_{\Omega_s} = 0, \quad \forall v_h \in V_h, \tag{3.10}$$

and the finite element discretization for Poisson equation is same as (3.8).

We decouple the nonlinear coupling system (3.7)-(3.8) with Gummel iteration [17]. In each iteration, the Poisson equation and each NP equation are solved successively. The ion concentrations are treated as known functions when solving the electrostatic potential, and vice versa. The process repeats until the difference of solutions in two adjacent iterations becomes smaller than a given tolerance.

For the steady-state case, in order to make iterations between the Poisson and SMNP equations converge, it is necessary to employ the under-relaxation technique, especially when macromolecules exist. In other words, solutions are updated with a linear combination of solutions respectively obtained from the last iteration and the current iteration, rather than just using solutions derived from the current iteration. This under-relaxation scheme [30,31,42] is described by

$$\begin{aligned} u^{\text{new}} &= \alpha u^{\text{old}} + (1 - \alpha) u^{\text{new}}, \\ c_i^{\text{new}} &= \alpha c_i^{\text{old}} + (1 - \alpha) c_i^{\text{new}}, \quad i = 1, 2, \dots, K, \end{aligned}$$

where the relaxation parameter $0 < \alpha < 1$ is a predefined constant. We note that without the under-relaxation technique, the iterations may not converge. More specifically, the iterative process will be presented in Section 4.

3.2 Inverse averaging technique

From the aforementioned content, if one wants to solve the finite element approximation equation (3.7) with the normal unknown variable c_i accurately, the numerical difficulty lies in dealing with the exponential coefficients $e^{-\Psi_l}$ and e^{Ψ_l} . In this subsection, an inverse averaging technique is developed for SMPNP equations to calculate the inverse averages of the exponential coefficients on the edge $E_{ij} = \overline{x_i x_j}$ of the element T . Especially, in order not to cause confusion and avoid using more notations, starting from this section, the index l in the formula represents the l th ion species, and other indexes, such as i, j, k refer to the node number on the element T .

3.2.1 The inverse average of the exponential coefficient

The inverse average of the exponential coefficient on the edge $E_{ij} = \overline{x_i x_j}$ is denoted with

$$E(\Psi)_{E_{ij}} = \left(\frac{\int_{x_i}^{x_j} e^{-\Psi} ds}{|E_{ij}|} \right)^{-1} \triangleq I(E_{ij}), \quad (3.11)$$

where Ψ is defined by (2.21) in this paper. In the other cases, Ψ may have its own specific definition, e.g. [48, 49]. The work [48] shows that the inverse averaging technique is significant to control the effect of large electrostatic fields on currents and enhance the stability of numerical methods for solving the standard PNP equations, particularly with rapidly varying coefficients when solving the three-dimensional drift-diffusion model in semiconductor device simulations. Inspired by this, we also use the inverse averaging technique to deal with the exponential coefficients in our work for solving the reformulated finite element approximation Eq. (3.7) when simulating biomolecular systems and ion channels.

Firstly, similar to [48], we also assume that Ψ is linear on the edge E_{ij} , that is

$$\Psi(\mathbf{x}) = \left(\frac{\Psi_j - \Psi_i}{|E_{ij}|} \right) (\mathbf{x} - \mathbf{x}_i) + \Psi_i, \quad \mathbf{x} \in [\mathbf{x}_i, \mathbf{x}_j]. \quad (3.12)$$

From (3.11) and (3.12), we get

$$\begin{aligned} I(E_{ij}) &= \left(\int_{x_i}^{x_j} \frac{e^{-\Psi_i}}{|E_{ij}|} \left(\frac{e^{\Psi_i}}{e^{\Psi_j}} \right)^{\frac{x-x_i}{|E_{ij}|}} dx \right)^{-1} = \left(\int_{x_i}^{x_j} \frac{e^{-\Psi_i}}{|E_{ij}|} e^{(\Psi_i - \Psi_j) \cdot \frac{x-x_i}{|E_{ij}|}} dx \right)^{-1} \\ &= \left(\frac{e^{-\Psi_i}}{\Psi_i - \Psi_j} \int_{x_i}^{x_j} e^{(\Psi_i - \Psi_j) \cdot \frac{x-x_i}{|E_{ij}|}} d \left(\frac{(\Psi_i - \Psi_j)(\mathbf{x} - \mathbf{x}_i)}{|E_{ij}|} \right) \right)^{-1} \\ &= \left(\frac{e^{-\Psi_i}}{\Psi_i - \Psi_j} e^{(\Psi_i - \Psi_j) \cdot \frac{x-x_i}{|E_{ij}|}} \Big|_{x_i}^{x_j} \right)^{-1} \\ &= e^{\Psi_i} B(\Psi_i - \Psi_j), \end{aligned} \quad (3.13)$$

where $B(t)$ is the Bernoulli function defined by

$$B(t) = \begin{cases} \frac{t}{e^t - 1}, & t \neq 0, \\ 1, & t = 0. \end{cases}$$

For numerical stability, if the difference between two nodal values of Ψ_i is very small, the corresponding terms “ $B(\Psi_i - \Psi_j)$ ” should be calculated using Taylor expansions. For more details, please refer to [48] and the references therein. Especially, the Bernoulli function $B(t)$ is calculated by

$$B(t) = \begin{cases} \frac{t}{e^t - 1}, & |t| > 10^{-4}, \\ \left(\left(-\frac{1}{720}t^2 + \frac{1}{12} \right) t - \frac{1}{2} \right) t + 1, & \text{otherwise,} \end{cases}$$

in our computation.

3.2.2 Inverse averaging finite element scheme for the reformulated SMNP equations

Now we give a derivation of the IAFEM for the reformulated Eq. (3.7). First of all, referring to the mean value theorem of integrals and approximating the exponential coefficient $e^{-\Psi}$ with $E(-\Psi)_{E_{ij}}$ on the edge E_{ij} of the element T , we have

$$\begin{aligned} 0 &= (D_l e^{-\Psi_{l,h}} \nabla(e^{\Psi_{l,h}} c_{l,h}), \nabla v_h)_{\Omega_s} \\ &= \int_{\Omega_s} D_l e^{-\Psi_{l,h}} \nabla(e^{\Psi_{l,h}} c_{l,h}) \cdot \nabla v_h d\Omega_s \\ &= \sum_{T \in \mathcal{T}_h} \int_T D_l e^{-\Psi_{l,h}} \nabla(e^{\Psi_{l,h}} c_{l,h}) \cdot \nabla v_h dT \\ &\approx \sum_{T \in \mathcal{T}_h} D_l E(-\Psi)_{E_{ij}} \int_T \nabla(e^{\Psi_{l,h}} c_{l,h}) \cdot \nabla v_h dT. \end{aligned} \tag{3.14}$$

In the following content, we introduce the computation of the element-wise stiffness matrix for (3.14), i.e., $A = (a_{ij}^T)_{T \in \mathcal{T}_h}$, in detail.

On a element T , let v_h take the associated piecewise linear finite element basis function. By using (3.6), we have

$$\begin{aligned} &D_l E(-\Psi)_{E_{ij}} \int_T \nabla(e^{\Psi_{l,h}} c_{l,h}) \cdot \nabla v_h dT \\ &= D_l E(-\Psi)_{E_{ij}} \sum_{x_j \in T} (e^{\Psi_{l,h}} c_{l,h})(x_j) \int_T \nabla \phi_j \cdot \nabla \phi_i dT \\ &= D_l E(-\Psi)_{E_{ij}} \sum_{x_j \in T} (e^{\Psi_{l,h}} c_{l,h})(x_j) e_{ij}^T \\ &= -D_l \sum_{x_j \in T, x_j \neq x_i} E(-\Psi)_{E_{ij}} ((e^{\Psi_{l,h}} c_{l,h})(x_i) - (e^{\Psi_{l,h}} c_{l,h})(x_j)) e_{ij}^T. \end{aligned} \tag{3.15}$$

Furthermore, the approximated coefficient $E(-\Psi)_{E_{ij}}$ is calculated by (3.13) on the edge E_{ij} , then we get

$$\begin{aligned}
& D_l E(-\Psi)_{E_{ij}} \int_T \nabla(e^{\Psi_{l,h}} c_{l,h}) \cdot \nabla v_h dT \\
&= -D_l \sum_{x_j \in T, x_j \neq x_i} E(-\Psi)_{E_{ij}} ((e^{\Psi_{l,h}} c_{l,h})(x_i) - (e^{\Psi_{l,h}} c_{l,h})(x_j)) e_{ij}^T \\
&= - \sum_{x_j \in T, x_j \neq x_i} D_l e^{-\Psi_{l,h}} B(\Psi_j - \Psi_i) (e^{\Psi_{l,h}} c_{l,h})(x_i) e_{ij}^T \\
&\quad + \sum_{x_j \in T, x_j \neq x_i} D_l (e^{-\Psi_{l,h}} B(\Psi_i - \Psi_j) (e^{\Psi_{l,h}} c_{l,h})(x_j) e_{ij}^T \\
&= \left(- \sum_{x_j \in T, x_j \neq x_i} D_l B(\Psi_j - \Psi_i) e_{ij}^T \right) c_{l,h}(x_i) + \sum_{x_j \in T, x_j \neq x_i} \left(D_l B(\Psi_i - \Psi_j) e_{ij}^T \right) c_{l,h}(x_j). \quad (3.16)
\end{aligned}$$

The nonzero entries of the element-wise stiffness matrix $A = (a_{ij}^T)_{T \in \mathcal{T}_h}$ can be written as

$$a_{ij}^T = \begin{cases} D_l B(\Psi_i - \Psi_j) e_{ij}^T, & j \neq i, \\ - \sum_{k \neq i} D_l B(\Psi_k - \Psi_i) e_{ik}^T, & j = i, \end{cases}$$

where

$$e_{ij}^T = \int_T \nabla \varphi_j \cdot \nabla \varphi_i dT,$$

and $\varphi_i, i = 1, \dots, N_h$ are nodal basis functions in V_h , which satisfy (3.3).

4 Numerical tests and application in simulating biomolecular systems and ion channels

In this section, we will use the IAFEM to solve the SMPNP (PNP) equations for simulating biomolecular systems and ion channels. To demonstrate the accuracy and robustness of the IAFEM, a model problem with analytic solutions on a cube is firstly tested. Then the size-effect simulations on a biomolecular sphere with different charges and an ion channel are respectively implemented. All the numerical algorithms are implemented based on the three-dimensional parallel finite element toolbox Parallel Hierarchical Grid (PHG) [47]. The computations were done on the high performance computers of State Key Laboratory of Scientific and Engineering Computing, Chinese Academy of Sciences.

As mentioned above, the Gummel iterative method is used to decouple the nonlinear coupling system (3.7)-(3.8), and also used for solving the traditional finite element approximation (3.8) and (3.10). In order to clearly understand the Gummel iterative process and calculation process in this work, we present the iterative process with IAFEM in

Algorithm 1: Gummel iteration for SMPNP equations with IAFEM

```

1 Step 1: Initialization for nonlinear iteration:
2   Initialize error tolerance tol and maximize iteration number max_N ;
3   Initialize iterative step counter n = 0;
4   Initialize electrostatic potential  $u_h^n = 0$ ;
5   for each  $i \in 1, 2, \dots, K$  do
6     Initialize concentration  $c_{i,h}^n = 0$  and auxiliary variable  $c_{i,h}^{n+1} = 0$ ;
7   end for
8 Step 2: Nonlinear iteration:  $n \geq 1$ , solving the decoupled equations:
9 while  $\|u_h^{n+1} - u_h^n\| > tol$  and  $j \leq max\_N$  do
10  |
11  |  $(\epsilon \nabla u_h^{n+1}, \nabla w_h)_\Omega = \left( \beta e_c^2 \lambda \sum_i^K z_i c_{i,h}^{n+1}, w_h \right)_\Omega - \beta e_c \left( \epsilon_m \frac{\partial(\phi^s + \phi^h)}{\partial \vec{n}}, w_h \right)_{\Gamma_m},$  (3.17)
12  |
13  |  $\Psi_{i,h}^n = z_i u_h^n - k_i \ln \left( 1 - \sum_l^K a_l^3 c_{l,h}^n \right), \quad k_i = a_i^3 / a_0^3,$  (3.18)
14  |
15  |  $(D_i e^{-\Psi_{i,h}^n} \nabla (e^{\Psi_{i,h}^n} c_{i,h}^{n+1}), \nabla v_h)_{\Omega_s} = 0,$  (3.19)
16  |
17  | if  $\|u_h^{n+1} - u_h^n\| < tol$  then
18  | | break;
19  | else
20  | |  $u_h^{n+1} \leftarrow \alpha u_h^n + (1 - \alpha) u_h^{n+1};$ 
21  | |  $c_{i,h}^{n+1} \leftarrow \alpha c_{i,h}^n + (1 - \alpha) c_{i,h}^{n+1};$ 
22  | end
23  |  $n \leftarrow n + 1;$ 
24 end
25 Step 3: Output the electrostatic potential  $\phi_h^{n+1} := u_h^{n+1} / (\beta e_c)$  and concentrations  $c_{i,h}^{n+1}$ .

```

Algorithm 1. Similarly, the nonlinear iterative process of the traditional FEM for SMPNP equations is presented in Algorithm 2.

In the following, some numerical experiments are reported to verify the effectiveness and robustness of the IAEEM for solving SMPNP equations. At first, a model problem with analytic solutions is presented to numerically verify the accuracy and convergence order of the new scheme. Then, a sphere model and an ion channel system are separately considered.

Algorithm 2: Gummel iteration for SMPNP equations by FEM

```

1 Step 1: The same as step 1 in Algorithm 1;
2 Step 2: Nonlinear iteration:  $n \geq 1$ , solving the coupled equations:
3 while  $\|u_h^{n+1} - u_h^n\| > tol$  and  $n \leq max\_N$  do
4   Step 2.1 Solving Poisson equation for  $u_h^{n+1}$  through Eq. (3.17);
5   Step 2.2 Solving SMNP equations for  $c_{i,h}^{n+1}$  through the following equation
      
$$\left( D_i \left( \nabla c_{i,h}^{n+1} + z_i c_{i,h}^{n+1} \nabla u_h^n + \frac{k_i c_{i,h}^{n+1}}{1 - \sum_l a_l^3 c_{l,h}^n} \sum_l a_l^3 \nabla c_{l,h}^n \right), \nabla v_h \right)_{\Omega_s} = 0, \quad (4.1)$$

6   if  $\|u^{n+1} - u^n\| < tol$  then
7     break;
8   else
9      $u_h^{n+1} \leftarrow \alpha u_h^n + (1 - \alpha) u_h^{n+1};$ 
9      $c_{i,h}^{n+1} \leftarrow \alpha c_{i,h}^n + (1 - \alpha) c_{i,h}^{n+1};$ 
10  end
11   $n \leftarrow n + 1;$ 
12 end
13 Step 3: Output the electrostatic potential  $\phi_h^{n+1} := u_h^{n+1} / (\beta e_c)$  and concentrations  $c_{i,h}^{n+1}$ .

```

4.1 Accuracy and convergence tests

In this subsection, we report the numerical accuracy tests on the IAFEM for SMPNP equations through a model problem with analytic solutions.

Example 4.1. In this example, we consider a model problem with analytic solutions on a cube. Let the computational domain $\Omega = [0, 1]^3$, and two charged species are considered in the system. Specially, we use c_p and c_n to denote the positive and negative concentrations respectively in this test, and their diffusion coefficients are $D_p = 0.196$, $D_n = 0.203$. Consider the following dimensionless SMPNP model problem

$$\begin{cases} -\nabla \cdot (\nabla u) = (c_p - c_n) + f_u, & \text{in } \Omega, \\ -\nabla \cdot D_p (\nabla c_p + c_p \nabla u + \frac{k_p c_p}{1 - \gamma \sum_l a_l^3 c_l} \sum_l a_l^3 \nabla c_l) = f_p, & \text{in } \Omega, \\ -\nabla \cdot D_n (\nabla c_n - c_n \nabla u + \frac{k_n c_n}{1 - \gamma \sum_l a_l^3 c_l} \sum_l a_l^3 \nabla c_l) = f_n, & \text{in } \Omega, \end{cases} \quad (4.2)$$

where $k_i = a_i^3 / a_0^3$ ($i = p, n$) with $a_0 = 3.1$, $a_p = 1.51$, $a_n = 2.37$, and $\gamma = 6.022140857 \times 10^{-4}$. The right-hand functions f_u, f_p, f_n and the boundary conditions are respectively given

Table 1: L^2 and H^1 errors of the IAFEM for SMPNPEs (Example 4.1).

h	$\ u_h - u\ _0$	Order	$\ c_{p,h} - c_p\ _0$	Order	$\ c_{n,h} - c_n\ _0$	Order
1/4	6.1793E-02	—	8.0782E-02	—	1.3742E-01	—
1/8	1.9120E-02	1.69	6.2609E-02	0.37	9.6801E-02	0.51
1/16	5.0597E-03	1.92	1.9858E-02	1.66	3.8814E-02	1.32
1/32	1.2967E-03	1.96	5.2659E-03	1.91	1.1011E-02	1.82
1/64	3.3956E-04	1.93	1.3353E-03	1.98	2.9460E-03	1.90
1/128	8.7309E-05	1.96	3.3437E-04	2.00	7.4430E-03	1.98
h	$\ u_h - u\ _1$	Order	$\ c_{p,h} - c_p\ _1$	Order	$\ c_{n,h} - c_n\ _1$	Order
1/4	4.5797E-01	—	1.0250E+00	—	3.1852E+00	—
1/8	1.8227E-01	1.33	9.0683E-01	0.18	2.2351E+00	0.51
1/16	8.1152E-02	1.17	3.5981E-01	1.33	9.2410E-01	1.27
1/32	3.9094E-02	1.05	1.5825E-01	1.19	3.8890E-01	1.25
1/64	1.9352E-02	1.01	7.5885E-02	1.06	1.8214E-01	1.09
1/128	9.6521E-02	1.00	3.7521E-02	1.02	9.0360E-02	1.01

by the following analytic solutions

$$\begin{cases} u = \sin(\pi x) \sin(\pi y) \sin(\pi z), \\ c_p = \sin(2\pi x) \sin(2\pi y) \sin(2\pi z), \\ c_n = \sin(3\pi x) \sin(3\pi y) \sin(3\pi z). \end{cases} \quad (4.3)$$

In this example, the piecewise linear finite element basis functions are used to discretize the SMPNP model (4.2). The L^2 norm and H^1 norm errors are reported in Table 1. The first column represents the mesh size of the uniform meshes. The numerical errors in L^2 norm and H^1 norm are second-order and first-order reduction, respectively. This numerically demonstrates the convergence accuracy and reliability of the IAFEM for solving SMPNP equations.

4.2 Simulation on a molecular sphere model

In this subsection, we will use the IAFEM to solve the SMPNP/PNP equations on a sphere model. These tests capture the fundamental difference between the SMPNP model and the classical PNP model. In the sphere model, a sphere with a negative charge in the center is used to simulate the solute molecule. The geometry and mesh of the sphere model are shown in Fig. 2, where $R = 80\text{\AA}$, $r = 10\text{\AA}$. Particularly, for the convenience of description and distinguish for the different positive and negative ions, in the following, the symbols K^+ , Na^+ , and Cl^- are used to refer to two different cations and anions.

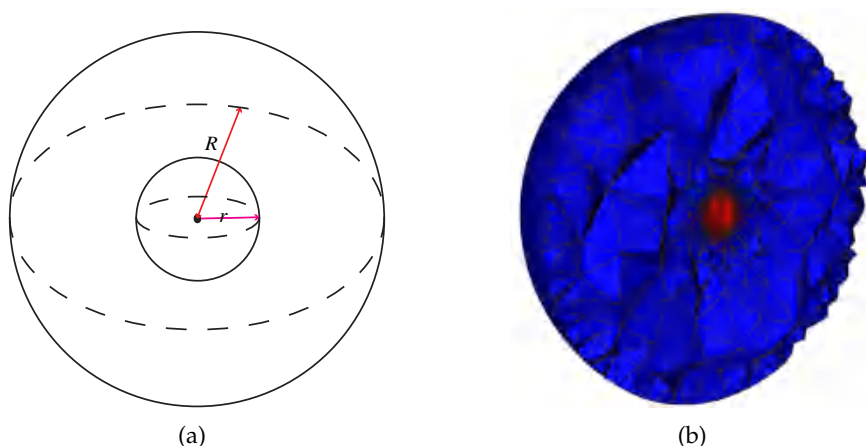


Figure 2: Schematic of the geometry (a) and mesh (b) of the sphere model.

- **Case 1:**

To evaluate the effectiveness and robustness of the IAFEM in bimolecule simulations, both SMPNP and PNP ($k_i=0$, see (2.7)) equations are solved by setting different negative charges in the center of the molecular sphere. We first consider a 1 : 1 KCl solution in our sphere model, where the bulk concentration $c_{bulk} = 0.1M$ and the applied potential $\phi_0=0V$. The negative charges in the center of the sphere are set as: $q_1 = -10e_c$, $q_2 = -20e_c$, $q_3 = -30e_c$, $q_4 = -35e_c$, $q_5 = -40e_c$, and $q_6 = -45e_c$, where e_c is the elementary charge.

Our previous numerical experience shows that the traditional finite element schemes for solving PNP equations often lead to nonphysical oscillations (negative concentration values) in practical computations, e.g. see [45]. As we all know, in the simulation of the molecular spheres, the counter-ion concentration near the surface of the molecular sphere increases as charges on the sphere accumulate. The counter-ion (K^+) concentrations with different charge quantity on the center sphere solved from the classical PNP equations with the standard finite element method (FEM) and IAFEM are respectively displayed in Fig. 3. When using the FEM to solve the PNP equations, Fig. 3(a) shows that the counter-ion concentration appears layer as the amount of charge increases to a certain value, e.g., $q_4 = -35e_c$, $q_5 = -40e_c$, $q_6 = -45e_c$. However, it's an impossible phenomenon for a single univalent ion without competition in these mean field models (the counter-ion concentration should decrease monotonically in this case). In other words, these layers are nonphysical solutions caused by traditional FEM. Especially, Fig. 3(a) also shows that the results of FEM start from zero. This is because the convection dominated is enhanced when the amount of charge increases to a certain value, and the traditional finite element scheme cannot control the nonphysical oscillation (the negative value) caused by the convection dominance. The the negative part is rounded off and the truncation is made at the zero when saving the value. Compared to Fig. 3(a), it is apparent from Fig. 3(b) that the curves of the counter-ion concentrations are always monotonous as the

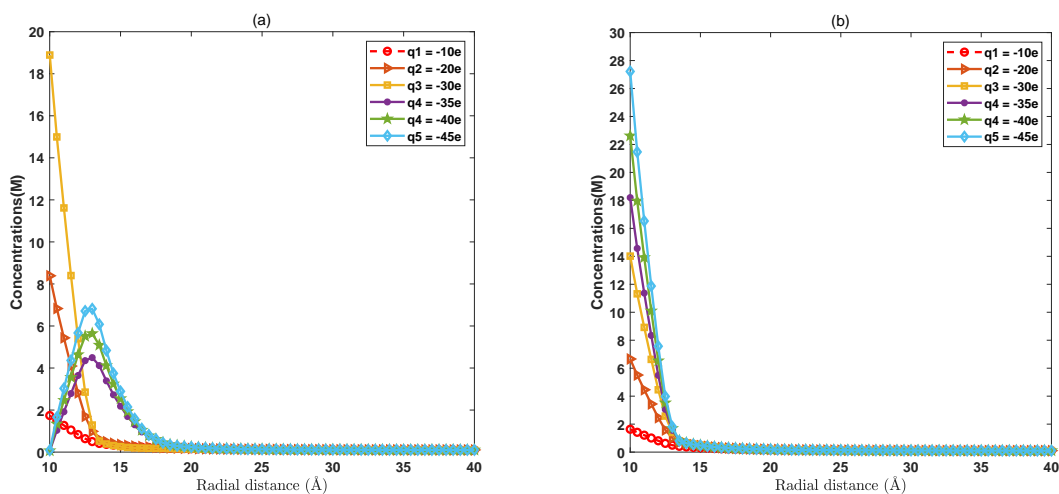


Figure 3: Cation (K^+) distributions near the surface of the sphere under different charges based on PNP equations which are solved by FEM (a) and IAFEM (b).

amount of charges increases. And the concentration value decreases rapidly to the bulk concentration value with the increase of the radial distance.

- **Case 2:**

Similarly, in order to demonstrate the effectiveness of the IAFEM for solving the SMPNP model in biomolecule simulations. In this case, we choose the ion size of cation and anion as $a_K = 2.51 \text{ \AA}$ and $a_{Cl} = 6.37 \text{ \AA}$, respectively, and the other parameters are the same as that mentioned in **Case 1**. The numerical results are shown in Fig. 4. The curves in (a) are obtained from FEM with the standard scheme (3.10) for SMNP equations, and the curves in (b) are computed with IAFEM. Similarly, it is observed from Fig. 4(a) that there also exist layers (nonphysical solutions) when solving SMPNP equations with FEM when the amount of charge increases bigger than a certain value. This illustrates that the SMPNP equations almost degenerate to PNP equations for counterion when the size of the counterion is less than the size of the solvent molecule. Fig. 4(b) shows that if the IAFEM is used to solve the SMPNP equations, the layer will not appear even if the quantity charges is high. The effectiveness and robustness of the IAFEM are further verified for solving SMPNP/PNP equations in biomolecule simulation. In addition, comparing with Fig. 3(b), from Fig. 4(b), it is seen that the counter-ion concentration solved from SMPNP equations is less than that obtained from PNP equations at the same amount of charges because of the ion size-effects. Specially, it can be seen from Figs. 3-4 that the numerical results near the surface of the sphere for the FEM and IAFEM are not completely consistent for the small central charges $-10e_c$, $-20e_c$, and $-30e_c$, which may be caused by the lack of the finer mesh. On the other hand, since this is a practical application simula-

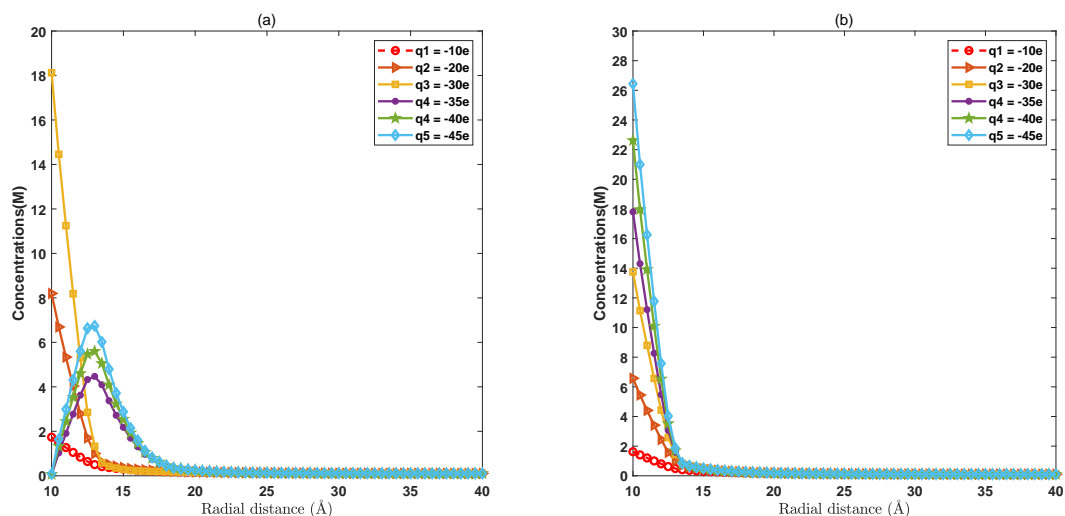


Figure 4: Cation (K^+) distributions near the surface of the sphere under different charges based on SMPNP equations which are solved by FEM (a) and IAFEM (b). The solvent molecular size is 3.1\AA , the counterion and coion size are $a_K = 2.51\text{\AA}$ and $a_{Cl} = 6.37\text{\AA}$, respectively. The ionic bulk densities are $0.1M$.

tion problem without an exact solution and two completely different numerical schemes are used, we do find that the numerical value of the IAFEM is slightly smaller than that of FEM. The deeper reasons shall be studied in our next work for more PNP-like equations.

We know that the ion size effect has a certain inhibitory effect on the ion concentration distribution [30]. In order to further reflect the influence of the ion size-effects on counterion concentration distributions, we fix the center charge of the sphere $q = -20e_e$ and the anion size $a_{Cl} = 6.37\text{\AA}$. Then the concentration distributions of counterions are studied by changing the size of the counterions. The results based on the PNP equations and SMPNP equations with different counterions sizes are listed in Fig. 5. These models are solved by IAFEM. When the ion size is larger, the concentration of the counterion near the surface of the sphere is smaller because of the inhibition of ion size effects.

• Case 3:

In this test, a 1 : 1 : 2 mixed solution of Na^+ , K^+ and Cl^- is taken into account, in which the bulk concentration is $c_{Na^+} = c_{K^+} = 0.1M$, $c_{Cl^-} = 0.2M$, and the diffusion coefficients are $D_{Na^+} = 0.133\text{\AA}/s$, $D_{K^+} = 0.196\text{\AA}/s$, $D_{Cl^-} = 0.203\text{\AA}/s$ for Na^+ , K^+ and Cl^- , respectively. For the ion size, we consider the hydration layer diameter of ions, that is $a_{Na^+} = 4.79\text{\AA}$, $a_{K^+} = 5.51\text{\AA}$, $a_{Cl^-} = 6.37\text{\AA}$ (cf. [24, 35]). Similar to **Case 1**, we investigate the convergence of the traditional FEM and IAFEM with various quantities of charges in the center of the sphere. In particular, in order to eliminate the influence of relevant factors of Gummel iteration on iterative convergence, we set the relaxation parameter $\alpha = 0.1$.

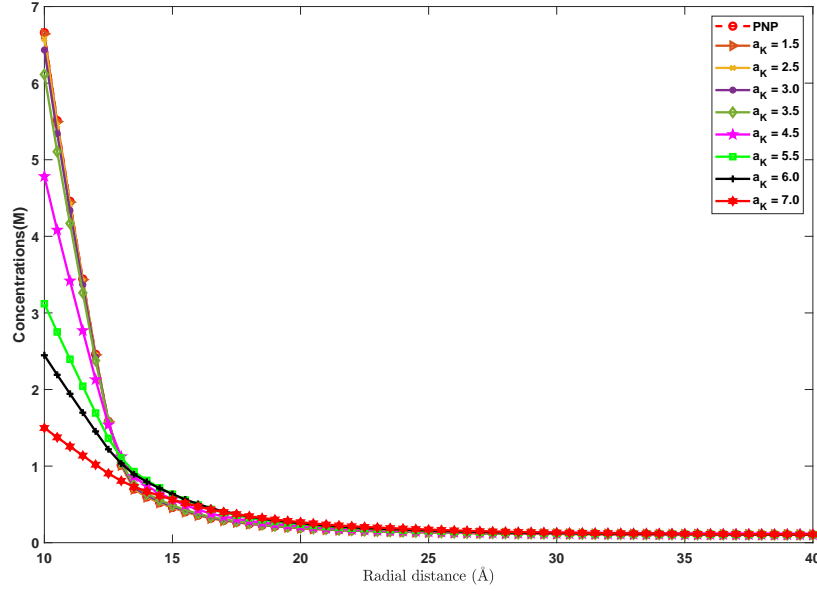


Figure 5: Cation (K^+) distributions near the surface of the sphere based on PNP equations (dashed line) and SMPNP equations under different counterion size (solid lines). Both the PNP and SMPNP equations are solved by IAFEM. The solvent molecular size is 3.1\AA , the coion size $a_{Cl}=6.37\text{\AA}$. The ionic bulk densities are $0.1M$.

Table 2: The convergence of Gummel iteration (convergence: \checkmark , non-convergence: \times).

q	$-10e_c$	$-20e_c$	$-25e_c$	\dots	$-28e_c$	$-29e_c$	$-30e_c$	$-35e_c$	$-38e_c$
FEM	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\times	\times	\times	\times
IAFEM	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark

The error tolerance tol is set as 1.0×10^{-6} . If $\frac{\|u - u_{old}\|_2}{\|u\|_2} < tol$, which represents the nonlinear iterative convergence, then the computation stops. The convergence results for FEM and IAFEM with different amounts of charges in the center of the sphere are listed in Table 2, where the notations " \checkmark " and " \times " represent whether the Gummel iteration has converged. The ellipsis (\dots) in the fifth column represents that the Gummel iteration can converge normally when the quantity of charges is in the interval $(-25e_c, -28e_c)$ both for the traditional FEM and IAFEM. Compared with the traditional FEM, Table 2 indicates that the IAFEM can simulate the highly charged molecular sphere with the size effect of the hydration layer of ions for a mixed solution.

Furthermore, in order to investigate the influence of the size effect of the counterion on the robustness of our methods, we set the charge amount $q = -20e_c$ and the size of the

Table 3: The convergence of Gummel iteration (convergence: \checkmark , non-convergence: \times).

$(a_{Na^+}, a_{K^+})(\text{\AA})$	(4.79,5.51)	(5.79,6.51)	(6.79,7.51)	(7.79,8.51)	(8.79,9.51)
FEM	\checkmark	\checkmark	\checkmark	\checkmark	\times
IAFEM	\checkmark	\checkmark	\checkmark	\checkmark	\checkmark
$(a_{Na^+}, a_{K^+})(\text{\AA})$	(9.79,10.51)	(10.79,11.51)	(11.79,12.51)	(12.79,13.51)	
FEM	\times	\times	\times	\times	
IAFEM	\checkmark	\checkmark	\checkmark	\checkmark	

coion $a_{Cl} = 6.37 \text{\AA}$, and the SMPNP equations are solved based on FEM and IAFEM with various sizes of the counter-ions. We choose the hydration layer diameter of Na^+ and K^+ , that is $(a_{Na^+}, a_{K^+}) = (4.79 \text{\AA}, 5.51 \text{\AA})$, as the starting point and increase the ion size by one unit (1\AA) at a time. The convergence results of the traditional FEM and IAFEM are reported in Table 3. It is seen from Table 3 that the IAFEM can simulate the SMPNP equations with the strong counter-ion size effect (the counter-ion size is greater than 10\AA) under some proper conditions. However, the traditional FEM can solve the SMPNP equations only with weak counterion size effects under the same conditions. These numerical experiments further verify the robustness and effectiveness of the IAFEM for solving the SMPNP equations with large-size effects in biomolecule simulations.

4.3 Size-effects in ion transports: a numerical simulation of a gA channel

In this subsection, we use the IAFEM to solve the SMPNP equations and PNP equations in the simulation of an ion channel. Gramicidin A (gA) is a well-characterized short polypeptide including hundreds of atoms with a helix structure. Fig. 6 shows a schematic picture of a single gA channel embedded in the lipid bilayer. This peptide is relatively easy to be synthesized and manipulated, compared with a typical sodium channel which has thousands of atoms. The gA channel is also relatively stable, therefore, it has been widely applied in biochemical and biophysical studies. Upon head to head dimerization, gA forms an elongated channel in the lipid bilayer that is permeable to small monovalent cations [44].

In our work, we utilize the SMPNP and PNP equations to calculate the concentration distributions of the cations in the channel. The size effects on the ion concentration distributions in the channel are further studied for different ions. In our computation, the gA channel system setup is similar to the model presented in [42]. The whole domain of the gA channel consists of the membrane protein region, bulk region, and channel region. The gA channel region is along the z -direction. The schematic of the simulation box and the gA channel meshes are shown in Figs. 7 and 8. In our simulations, the box size is $[-50 \text{\AA}, 50 \text{\AA}]^3$, the channel region is $[-14 \text{\AA}, 7 \text{\AA}]$, and the total number of tetrahedral elements is 92480.

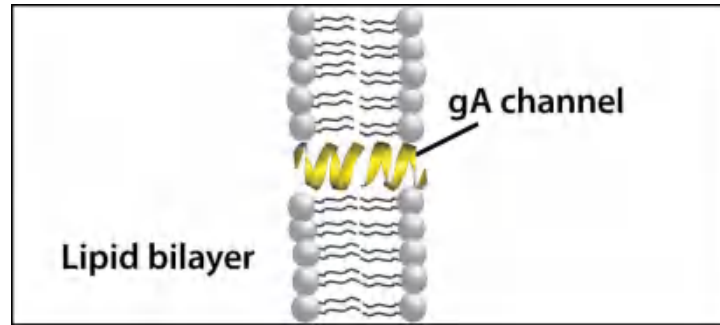


Figure 6: A schematic picture of a single gramicidin A pore embedded in a lipid bilayer (see [46]).

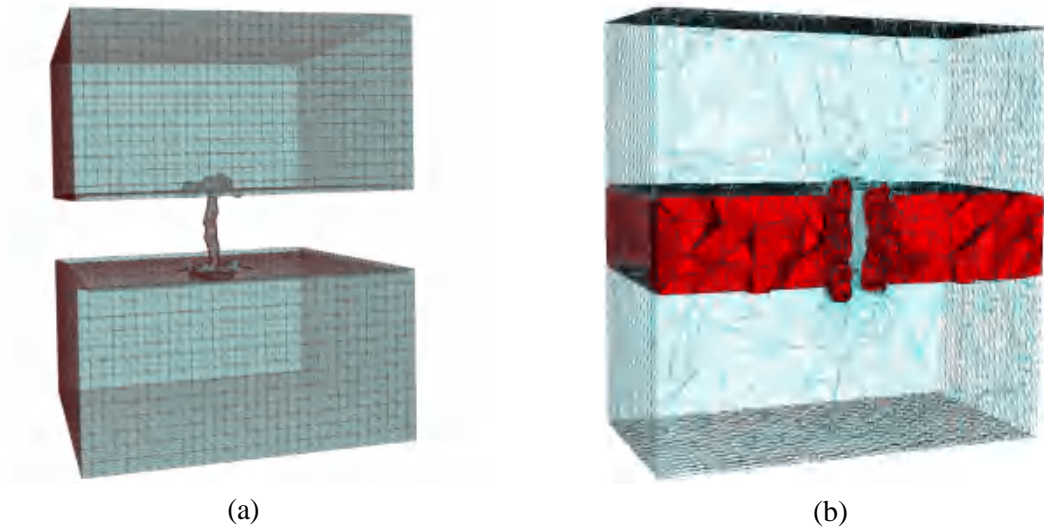


Figure 7: (a) The gA channel embedded in the simulation box. (b) A cut plane through the center of the simulation box along the z-axis.

- **Case 1:**

At first, similar to the sphere model, we consider a 1:1 KCl solution in our gA channel system, where the bulk concentration $c_{bulk}=0.1M$ is on the top and bottom of the box, and the potential $\phi_0 = -0.15V$ is applied with the potential difference along the z-direction. The diffusion coefficients for cation and anion, for example, K^+ and Cl^- , in the bulk region are set to their experimental values: $D_K = 0.196\text{\AA}^2/ps$, $D_{Cl} = 0.203\text{\AA}^2/ps$. While there is no experimental measurement of exact values for the diffusion coefficients inside the channel, it is known that the diffusion coefficients in the bulk region and the channel region should be different. In this work, the diffusion coefficients inside the channel are set by the same way as shown in [42]. In order to study the influence of size effects on the cation concentration distribution in the channel, both the PNP equations and SMPNP

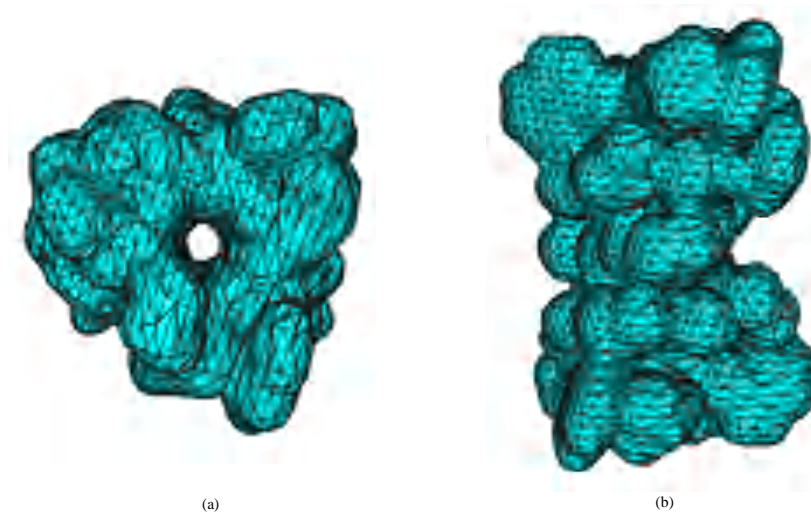


Figure 8: Schematic of the gA channel meshes: a) top view. b) lateral view.

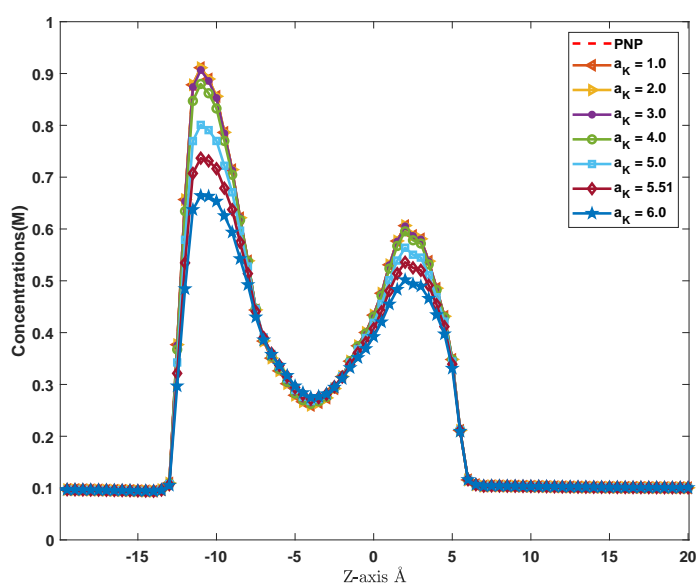


Figure 9: The cation density profile in the channel computed by PNP equations (dashed line) and SMPNP equations with different cation size (solid lines), where the anion size $a_{Cl} = 4.37 \text{ \AA}$, and the solvent molecular size $a_0 = 3.1 \text{ \AA}$.

equations with different ionic sizes are solved by the IAFEM for the gA system. The size of the anion (Cl^-) is fixed at 4.37 \AA , and the solvent molecular size $a_0 = 3.1 \text{ \AA}$. The cation size is arbitrarily given in this test. Fig. 9 shows the cation concentration profile in-

side the channel solved from PNP equations and SMPNP equations with different cation sizes. If the size of the cation is larger, the cation concentration in the channel obtained from SMPNP equations is lower compared with that solved from PNP equations. This is because the large size of the cation can strengthen the spatial repulsion of the model. Therefore, the SMPNP model, especially with large size effects, can be used to control the infinite increase of ion concentrations in the channel. For example, the ion currents matched with the experimental data (cf. [1–3]) can be obtained through numerical simulations with high bulk concentrations and high applied voltage difference, which will be studied in our next work.

- **Case 2:**

In this case, we consider the influence of the size effects on ion competitions in the channel. Similar to the test in **Case 3** of the biomolecular sphere model mentioned above, we still consider a 1 : 1 : 2 mixed salt solution for Na^+ , K^+ and Cl^- , in which the bulk concentration is $c_{Na^+} = c_{K^+} = 0.1M$, $c_{Cl^-} = 0.2M$, and the diffusion coefficients and the applied potential are the same as that in **Case 1**. In addition, the solvent molecular size and the anion size are respectively fixed as $a_0 = 3.1\text{\AA}$ and $a_{Cl} = 4.37\text{\AA}$. Both the PNP and SMPNP equations are solved via the IAFEM.

For SMPNP equations, to evaluate the influence of ion size effects on cation distributions in the channel, we arbitrarily change and increase the sizes of Na^+ and K^+ in our computation. It is worth noting that the actual size of K^+ is larger than the size of Na^+ , so we always make the ion size for K^+ one unit (1\AA) larger than the size for Na^+ at a time in the test. We considered the concentration distributions in the $g\text{\AA}$ channel along the z -axis. The numerical results are displayed in Fig. 10. The subfigure (a) is the concentration profile for Na^+ and K^+ obtained by PNP equations without the size effects, and the subfigures (b)-(f) show the concentration profile obtained from SMPNPEs with different ion sizes for Na^+ and K^+ . Fig. 10(a) demonstrates that the traditional PNP equations cannot distinguish the two cations with the same valence. In particular, for comparison, the concentration distributions computed through PNP equations are also shown in figures (b)-(f). It is observed from Fig. 10 that, similar to PNP equations, the ion distributions for Na^+ and K^+ calculated with SMPNP equations still cannot be distinguished in the channel when the ion size is small (see subfigures (b)-(d)). However, the subfigures (e)-(f) show that the concentration distributions of Na^+ and K^+ in the channel can be clearly distinguished by SMPNP equations when the cation size becomes larger. In addition, the concentration profiles from subfigures (e)-(f) also show that the concentration of K^+ is less than that of Na^+ , which indicates that the size of the ion can strengthen the size inhibition effect.

At last, in order to show the computational efficiency of IAFEM for solving the SMPNP equations in ion channel simulations, we select three different bulk concentrations (the applied potential ϕ_0 fixed as $100mV$) and applied potential (the bulk concentrations fixed as $0.1M$) to evaluate the CPU time of FEM and IAFEM, respectively. Here, the 1 : 1 : 2 mixed salt solution for Na^+ , K^+ and Cl^- is considered, and the ion size is

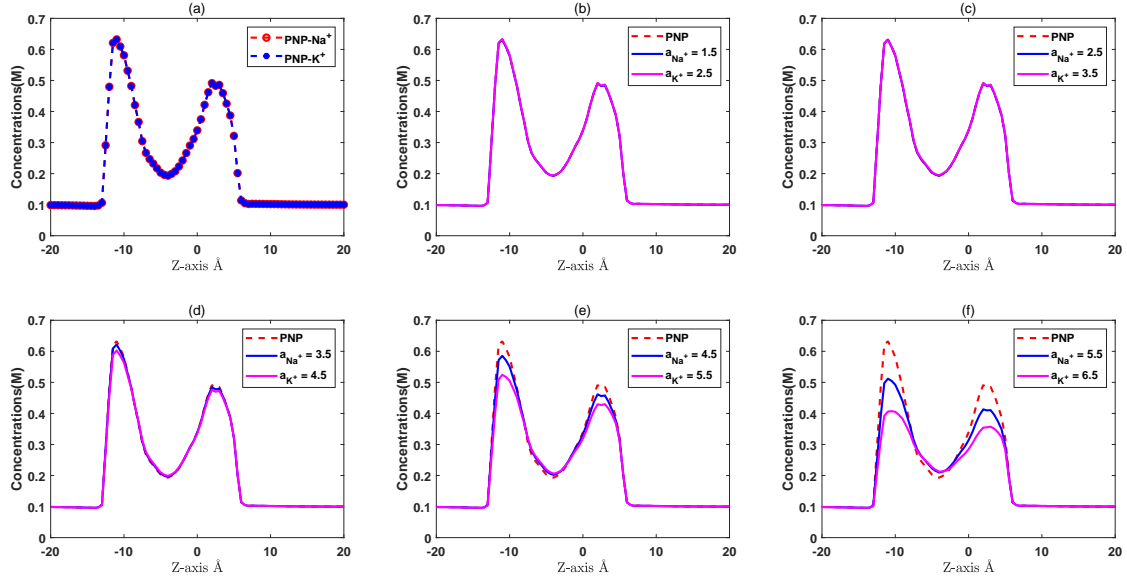


Figure 10: Cation distributions in the gA channel under a fixed membrane voltage ($\phi_0 = -0.15V$) and bulk concentration ($c_{Na^+} = c_{K^+} = 0.1M$, $c_{Cl^-} = 0.2M$) computed by PNP equations (dashed line) and SMPNP equations with different ion size (solid lines). (a): The ion distributions both for Na^+ and K^+ by PNP equations; (b)-(f): The ion distributions based on SMPNP equations with different cation size (solid lines). The anion size a_{Cl^-} and the solvent molecular size a_0 is fixed as 4.37\AA and 3.1\AA , respectively.

Table 4: The CPU time (seconds) of the FEM and IAFEM for solving the SMPNP equations in ion channel simulations.

ϕ_0	c_{bulk}	FEM	IAFEM	c_{bulk}	ϕ_0	FEM	IAFEM
100mV	0.1M	119.07	51.81	0.1M	50mV	113.31	50.56
	0.2 M	115.27	52.65		100mV	119.07	51.81
	0.3 M	121.60	51.23		150mV	116.13	51.69

set as $a_{Na^+} = 5.5\text{\AA}$, $a_{K^+} = 6.5\text{\AA}$, and $a_{Cl^-} = 4.37\text{\AA}$, respectively. The CPU time both for the FEM and IAFEM are reported in Table 4. It is seen from Table 4 that the CPU time cost of the IAFEM is almost half of that of the standard FEM whatever changing the bulk concentrations or applied potential.

5 Conclusion

In this work, we introduce a generalized Slotboom transformation and an IAFEM to solve the SMPNP equations. With the generalized Slotboom transform, the original SMNP equations are transformed into new reformulations which are self-adjoint equations with

exponentially behaved coefficients. Then the inverse averaging technique over the edges of the element can be used to deal with the exponential coefficients. Numerical experiments are reported to confirm the efficiency and robustness of the new schemes for SMPNP equations. Firstly, a model problem with analytic solutions on a cube box is tested to numerically verify the accuracy and order of the new schemes for SMPNP equations. Then, based on the averaging technique, simulations of both biomolecular sphere systems and ion channel systems are studied to demonstrate the effectiveness and robustness of the IAFEM for SMPNP equations. In particular, the averaging technique introduced in this paper can be easily extended to more complex PNP-like models for simulating biomolecular systems, such as the variable dielectric Poisson-Nernst-Planck (VDPNP) equations and Born-energy-modified PNP (BPNP) equations [27, 28], in which the dielectric coefficients depend on the ion concentrations and spatial positions, respectively. This will be studied in our future work. In addition, because of the strong coupling non-linearity of the system and the proposed scheme is based on the reformulation of the SMNP equations with exponential terms, the convergence analysis is not a matter of standard analysis. We leave it as the future work. Especially, the data that support the findings of this study are available within the article. The source code for this paper is available from <https://github.com/rgshen/SMPNP-IAFEM>.

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