

# Ion Distribution and Permeation Study of Biological Ion Channel Using PNP/ECP Model

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*Abstract:* The ion distribution inside a biological ion channel is crucial for the permeation properties of the system. The Poisson-Nernst-Planck (PNP) theory can be used to compute macroscopic current in ion channels efficiently. However conventional PNP theory is based on a continuum model for the charge flow, in which ions are considered as point particles. Due to the overscreening of mobile charge in the continuum model and the point simplification of ions, the conventional PNP theory predicts high ion concentration at highly charged protein and channel interface, but moderate ion concentration at the axis of the channel region. This unrealistic ion distribution results in the criticism of the PNP theory by many biologists for its inadequacy of explaining ion selectivity and current saturation phenomena observed in many ion channels. The PNP model can be modified to include effects of finite ion size and water occupation by including a correction term, the Excess Chemical Potential (ECP), into the standard model [6] (Gillespie et al., 2002). The ECP correction term is calculated from the Density Functional Theory (DFT). A coupled 3-D PNP/ECP model is developed to simulate ion transport in biological ion channels [16] (Zhicheng et al., 2005). Ion distribution in simple nanopore structure and real biological ion channels are presented in this paper. Permeation properties have been analyzed and compared to experiment results.

*Key-Words:* Ion Channel, Poisson-Nernst-Planck (PNP), Excess Chemical Potential (ECP), Density Functional Theory (DFT), Gramicidin A (GA), Selectivity

## 1. Introduction

Ion channels are aqueous pores formed by protein molecules. They are located in the membranes of the cell and can open and close to permit ion flow in and out of the cell. Ion channels consist of a chain of amino acids which carry strong permanent charges. The permanent charge has great influence on the behavior of ion channels. Molecular Dynamics (MD) is a complete approach for detailed ion channel simulation but computational requirements limit practical application to 100ns simulation times, making it still

impractical to resolve electrical currents on typical biological timescales. The Poisson-Nernst-Planck (PNP) theory, similar to the self-consistent Drift-Diffusion theory of solid-state devices, can be used to compute macroscopic currents in ion channels efficiently. However, PNP theory is based on a model that treats ions as a continuum fluid of point particles. Because of this, the charge interaction between fluid and pore walls is not same as one would expect with discrete mobile ions. Additionally, the conventional PNP theory cannot take into account the finite volume oc-

cupied by ions and water molecules, as well as the non-singular distribution of charge on the ion. As a result, Coulomb screening and ion packing can be overestimated, particularly in highly charged regions. Criticized by many researchers, the conventional PNP theory cannot describe specific ion selectivity phenomena observed in certain channels [8] from purely electrical features of the model. To describe ion transportation more realistically, size effects of ions and water molecules must be included in our model to form a more realistic ion distribution and potential profile. Excess Chemical Potential (ECP) correction is introduced to achieve this goal [11]. In this paper, the PNP/ECP model is introduced and its application to simple nanopore structure and gramicidin A (gA) channel are presented.

## 2 The PNP/ECP Model

### 2.1 PNP theory

In continuum theory, the flux  $J_i$  of the  $i^{th}$  ion species is described by the Nernst-Planck (NP) equation as below:

$$J_i = -(z_i e D_i / k_B T) \rho_i \nabla \mu_i \quad (1)$$

Here  $D_i$ ,  $z_i$ ,  $e$ ,  $\rho_i$ , and  $\mu_i$  are, respectively, the diffusion coefficient, valence of ion species  $i$ , electron charge, ion density of species  $i$ , and chemical potential of ion species  $i$ . The chemical potential  $\mu_i$  is the combinational effect of electrical potential and ion concentration, and can be expressed as:

$$\mu_i = z_i e \phi + k_B T \ln \rho_i \quad (2)$$

Here  $\phi$  is the electrical potential,  $k_B$  is the Boltzmann constant, and  $T$  is the temperature. Then Eq. (1) can be rewritten as:

$$J_i = -(z_i e^2 D_i / k_B T) \rho_i \nabla \phi - Z_i e D_i \nabla \rho_i \quad (3)$$

The electrical potential  $\phi$  in Eq. (2) (3) is determined by the Poisson equation

$$\epsilon_0 \nabla (\epsilon(r) \nabla \phi(r)) = - \sum_i z_i e \rho_i - \rho_{fixed} \quad (4)$$

Here  $\epsilon_0$  is the dielectric constant in vacuum,  $\epsilon(r)$  is the relative dielectric constant at place  $r$ , the sum over  $i$  gives the charge density associated with the mobile ions in the electrolyte, and  $\rho_{fixed}$  represents all the other fixed charges in the channel or on a boundary.

For the steady state we have  $\nabla J_i = 0$ . By operating  $\nabla$  on Eq. (3) and assuming constant diffusion coefficient, we get  $k$  second-order PDEs, where  $k$  is the total number of ion species.

$$\nabla^2 \rho_i + \frac{z_i e D_i}{k_B T} (\rho_i \nabla^2 \phi + \nabla \rho_i \nabla \phi) = 0 \quad (5)$$

The coupled Equations. (5) and (4) can be solved simultaneously for the potential, ion concentrations, and ion flux of an ion channel system.

### 2.2 ECP correction

To include the size effect of ions and water molecules as well as the non-singular charge distribution on the ions, an ECP correction term is introduced to the Drift-Diffusion equation

$$J_i = -(z_i e D_i / k_B T) \rho_i \nabla (\mu_i + \mu_i^{ex}) \quad (6)$$

Here  $\mu_i^{ex}$  is the Excess Chemical Potential (ECP), defined as:

$$\mu_i^{ex} = \mu_i^{HS}(\rho) + \mu_i^{ES}(\rho) \quad (7)$$

The ECP correction in Eq. (7) can be obtained from neighboring ion densities using Density Functional Theory [6] [10] [11]. Since water molecules have no net charge, it is not possible to use a continuity equation for charged particles to describe their contribution. To account the volume occupied by water molecules, we use the fact that the chemical potential for ions and water molecules in an electrolyte system should be uniform at equilibrium.

$$k_B T \ln(\rho_{c,w}) = k_B T \ln(\rho_{b,w}) + u_w^{ex}(\rho) \quad (8)$$

Where  $u_w^{ex}$  is the difference of ECP correction in bath and channel regions. Because  $u_w^{ex}$  is a function of water density, Eq. (7) and Eq. (8) are coupled equations to be solved simultaneously. To

describe the steady state of an ion channel, we need to include  $k$  Nernst-Planck equations Eq. (6) for  $k$  ion species,  $k + 1$  ECP correction equations Eq. (7) for  $k$  ion species and water molecule, one poisson equation Eq. (4), and one water density relation Eq (8).

### 2.3 The PNP/ECP model

To solve the overall PNP/ECP system of equations self-consistently, we use a decoupled algorithm for the ECP correction. Using an initial guess of the ECP correction, The discretized PNP equations are first solved using Newton's method and the resulting ion densities are used to calculate the corresponding ECP correction. The PNP system is solved repeatedly with successive updates of the ECP correction until convergence is obtained.

## 3 Results

### 3.1 Simulate 3-D test structure

A simplified 3-D nanopore sample, shown in Fig. 1, is constructed to test the PNP/ECP model. A dielectric slab represents a membrane separating two electrolyte baths each containing a 1M/L NaCl solution. A nanoscale opening with square cross-section of  $4.5\text{\AA} \times 4.5\text{\AA}$  provides a channel connecting the two baths across the membrane. A permanent charge profile is attached to the nanopore structure. The profile has two opposite charge rings with density of  $0.018 \times 10^9 \text{ C/m}$  near the entrance of the channel, shown in Fig. 1.

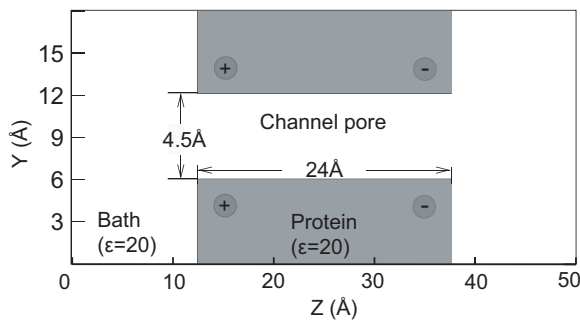


Figure 1: Simplified nanopore structure with two opposite charge rings near the entrance of the channel.

The positive charge ring is wrapped one grid away from the channel wall, on the cross-section close to the left opening of the channel. The negative line of charge with identical shape and density is wrapped at the image position close to the right opening of the channel. At equilibrium, conventional PNP theory yields geometrically symmetric sodium ion density and chlorine ion density, shown in Fig. 2(a) and Fig. 3(a).

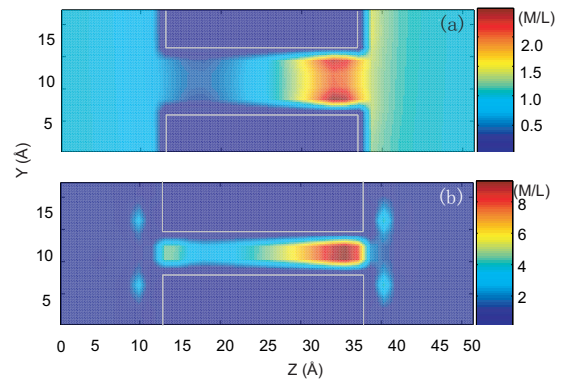


Figure 2: Density plot of  $\text{Na}^+$  in Y-Z plane cross the axis of nanopore structure, at equilibrium. Bath ion concentration is 1M/L. (a) Conventional PNP model. (b) PNP/ECP model.

This symmetric feature of the sodium ion and chlorine ion density roots from the fact that ions are treated as point charge in the conventional PNP model, in which different ions are differentiated from each other by the valence and mobility only. From Fig. 2(a) and Fig. 3(a), we see that both ions are attracted to the charged membrane/channel interface. This phenomena can be also explained by the point charge treatment of ions in the conventional PNP theory. When include the size effects of the ions, the PNP/ECP model shows that sodium ions cumulate at the axis of the channel region and chlorine ions have difficulty going into the channel region, shown in Fig. 3(b) and Fig. 2(b). As a result of positive charge accumulation in the channel, we find an increased density of anions in the bath regions close to the channel end to compensate for it, as shown in Fig. 3(b).

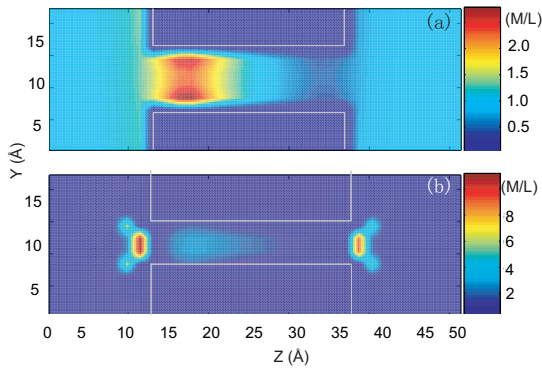


Figure 3: Density plot of  $\text{Cl}^-$  in Y-Z plane cross the axis of nanopore structure, at equilibrium. Bath ion concentration is 1M/L. (a) Conventional PNP model. (b) PNP/ECP model.

#### 4 Simulate the gramicidin A channel

Gramicidin A (gA) is currently one of the best understood channels experimentally and theoretically. It is formed by two monomers from each side of a lipid bilayers [3]. Each monomer has 15 amino acids folded into a helical structure [12]. gA has a small pore region with diameter of  $4.5\text{\AA}$  in the middle, which extending to  $5\sim 10\text{\AA}$  at the side chains [4] [5], shown in Fig. 4. gA is known to selectively conduct small monovalent cations ( $\text{H}^+$ ,  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ) and reject all anions [4] [5] [7] [15]. Recent NMR studies [14] [13] has showed that gA peptide remains rather rigid although earlier work proposed that plasticity of the structure is essential for ion transportation study. This justified the treatment of gA backbone structure as a charged and fixed confinement in the PNP/ECP model. In this section, we use the 1MAG atomic coordinates from Ketchum et al. [9], which can be download from Protein Data Bank (PDB) [1].

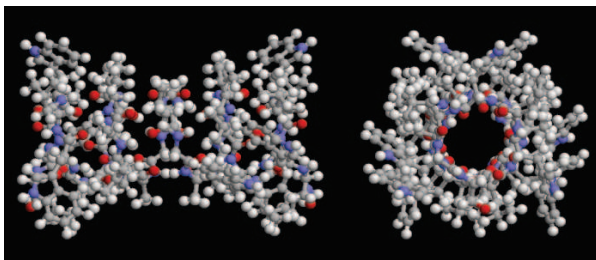


Figure 4: 3D visualization of the gA(1mag) channel using RasMol [2].

Figure. 5(a) and Figure. 6(a) show the ion densities for the conventional PNP theory and the PNP/ECP theory under equilibrium, with a bath ion concentration of 1 M/L. We can see that the traditional PNP model predicted a cation ( $\text{Na}^+$ ) relatively low density in the axis of the channel pore at the two highly charged binding sites [13]. This density is not high enough to form a high potential barrier to block out the anions from entering the channel pore region. Therefore can't eliminate the anion current when bias applied. The PNP/ECP model predicts a cation densities of approximate 60M/L for sodium ions at the highly charged binding sides, and close to zero anion density.

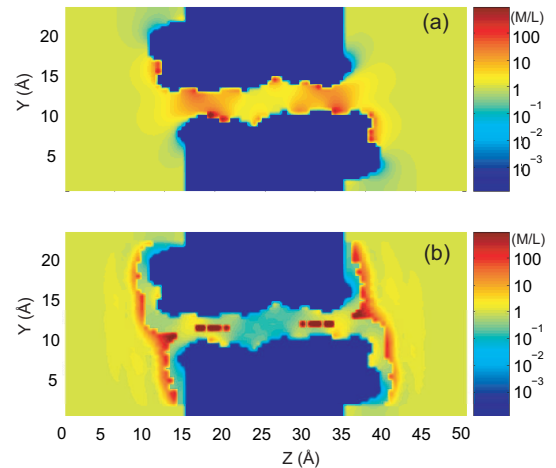


Figure 5: Cation density and ECP correction plots in Y-Z plane cross the axis of gA channel at equilibrium. Bath ion concentration is 1M/L. (a)  $\text{Na}^+$ , the conventional PNP theory. (b)  $\text{Na}^+$ , the PNP/ECP theory.

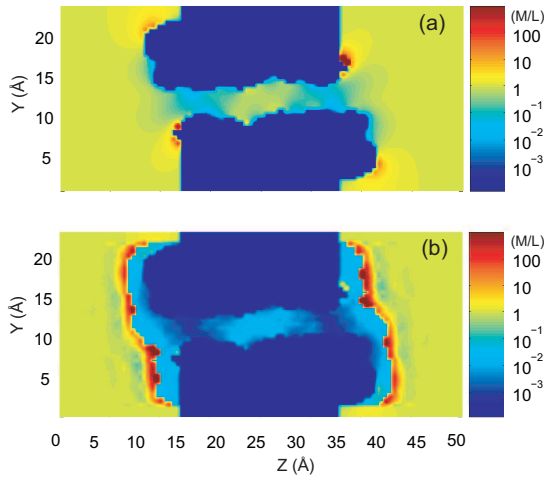


Figure 6: Anion density and ECP correction plots in Y-Z plane cross the axis of gA channel at equilibrium. Bath ion concentration is 1M/L. (a) Cl<sup>-</sup>, the conventional PNP theory. (b) Cl<sup>-</sup>, the PNP/ECP theory.

Figure. 7 and Figure. 8 show the I-V characteristic and I-C characteristic of gA channel. We see that the conventional PNP model predicts a higher current and no current saturation at high bath ion concentration, while the PNP/ECP model gives a good I-V and I-C characteristic curve which matches the experimental data well.

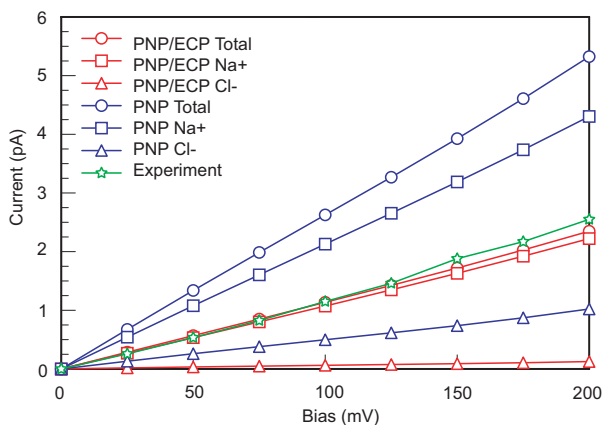


Figure 7: I-V characteristic comparison of gA channel for the conventional PNP model, the PNP/ECP model and experiment result. Bath ion concentration is 1M/L.

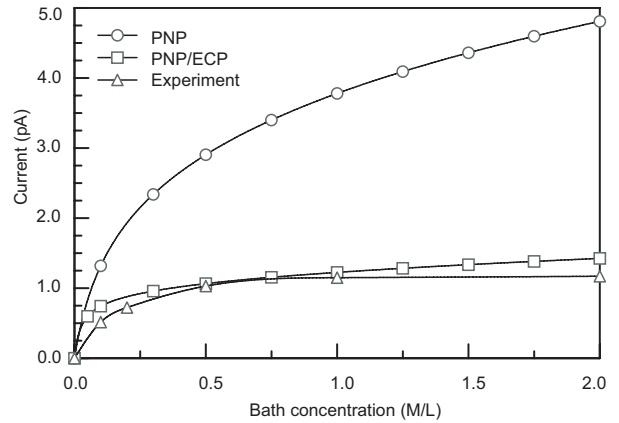


Figure 8: I-C characteristic comparison of gA channel for traditional PNP model, PNP/ECP model and experimental data at bias of 100mV

## 5. Summary and Conclusions

In this paper we discussed an efficient and justified 3-D semi-continuum model for ion channel simulation, examined the process of simulating ion channel using the PROPHET simulator. Test nanopore structure and real ion channel are simulated and permeation features are presented and analysed. Future improvement will be to include the dipole property of the water molecules into the PNP/ECP model, and compare with the Monte Carlo simulation.

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