

# Ion Channel Simulations Using the TR-PNP Model and the Excess Chemical Potential Approach

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## ABSTRACT

We describe a new method referred to as TR-PNP model to study general types of nanostructure ion channels. Our method extends the common continuum methods to include particle like properties, such as ion trapping and release effects. A previously known approach to deal with those effects is the excess chemical potential method. The Eyring rate theory is utilized to connect the two methodologies. We implement a toy channel model with single binding site in terms of both approaches, and demonstrate their equivalence under steady state conditions. Then we perform a time dependent simulation (timescale: $\mu\text{s}$ ) on another toy channel with two binding sites by using the TR-PNP model. Our results quantitatively illustrate the hopping process of ions from one site to the other. This method is therefore a good candidate to be integrated into a multi-scale simulation framework to provide a bridge between continuum and particle methods.

**Keywords:** ion channel, Poisson-Nernst-Planck (PNP), excess chemical potential (ECP), ion trapping and release, TR-PNP model

## 1 INTRODUCTION

Biological ion channels [1] are protein pores which regulate the flow of ions into and out of cells. The Poisson-Nernst-Planck (PNP) method [2][3] has been used to investigate the permeation properties of many ion channels. One impressive advantage of this method is its capability to simulate the fundamental mechanism of ion transport with relatively low computational demand. Its physics is equivalent to the self-consistent solution of the Poisson and drift-diffusion equations. The PNP method has achieved remarkable success by predicting some macroscopic characteristics such as current-voltage profiles (I-V curves). Details regarding the particle nature cannot be covered by this method. For example, ion trapping and release effects, which have been demonstrated to be crucial for a wide variety of channels (such as the KcsA potassium channel [4]), can not be addressed within the traditional PNP model. In this paper, we take these effects into account in terms of two different methodologies, the TR-PNP model that

we first proposed in [5] and the excess chemical potential (ECP) method used in [6][7]. Their relations are also discussed and it is shown that the TR-PNP model is superior for time-dependent simulations.

## 2 METHODS

### 2.1 TR-PNP Model

From a theoretical point of view, the equations commonly used in PNP simulations are not as complete as those used for semiconductors because they neglect the so-called generation recombination terms. This fact suggests to use terms that are analogous to Shockley's generation and recombination expressions [8][9] from semiconductor theory to model the trapping and release of ions. In an anion-selective channel, the anion trapping and release rate are given respectively as

$$R_- = c_- C_-^m (N_T - C_-^t) \quad (1)$$

$$G_- = e_- C_-^t \quad (2)$$

where  $C_-^m$ ,  $C_-^t$  denote mobile anion concentration and trapped anion concentration respectively. Three characteristic parameters are the total trap concentration  $N_T$ , the anion trapping coefficient  $c_-$  and the anion release coefficient  $e_-$ . This treatment has the advantage of capturing the effects of ion trapping and release phenomenologically by rate equations involving three adjustable parameters. As a result, the traditional PNP system of equations can be extended to the following equations:

$$\nabla \bullet (\epsilon \nabla \varphi) = q(C_{fixed} + C_+ - C_-^m - C_-^t) \quad (3)$$

$$\frac{\partial C_+}{\partial t} + \nabla \bullet \vec{F}_+ = 0 \quad (4)$$

$$\begin{aligned} \frac{\partial C_-^m}{\partial t} + \nabla \bullet \vec{F}_- &= G_- - R_- \\ &= e_- C_-^t - c_- C_-^m (N_T - C_-^t) \end{aligned} \quad (5)$$

$$\begin{aligned} \frac{\partial C_-^t}{\partial t} &= R_- - G_- \\ &= c_- C_-^m (N_T - C_-^t) - e_- C_-^t \end{aligned} \quad (6)$$

$$\vec{F}_+ = -\mu_+ C_+ \nabla \varphi - D_+ \nabla C_+ \quad (7)$$

$$\vec{F}_- = -\mu_- C_-^m \nabla \varphi + D_- \nabla C_-^m \quad (8)$$

where  $\varphi$  is the electrostatic potential,  $\epsilon$  the dielectric constant,  $q$  the elementary charge,  $C_{fixed}$  the concentra-

tion of fixed (permanent) charge lining the channel pore,  $\mu$  the mobility and  $D$  the diffusivity. We refer to the above model and system of equations by the acronym TR-PNP where “TR” means the inclusion of ion trapping and release effects. More details can be found in [5].

## 2.2 The Excess Chemical Potential Method

The ECP represents the free energy needed for an ion to occupy the particular binding site in the restricted environment inside the channel pore. In other words, it can be viewed as the offset in chemical potential which reflects the energy difference for an ion in the bulk and channel pore. Thus local chemical interactions including the trapping and release effects can be incorporated phenomenologically into this term. In addition to the concentration and electrical potential terms that are described by the drift-diffusion equation, an “excess” chemical potential  $\phi$  (different from the electrostatic potential  $\varphi$ ) is added. If attention remains focused on the case of anions, the system of equations becomes

$$\nabla \bullet (\epsilon \nabla \varphi) = q(C_{fixed} + C_+ - C_-) \quad (9)$$

$$\frac{\partial C_+}{\partial t} + \nabla \bullet \vec{F}_+ = 0 \quad (10)$$

$$\frac{\partial C_-}{\partial t} + \nabla \bullet \vec{F}_- = 0 \quad (11)$$

$$\vec{F}_+ = -\mu_+ C_+ \nabla \varphi - D_+ \nabla C_+ \quad (12)$$

$$\vec{F}_- = -\mu_- C_- \nabla (\varphi + \phi) - D_- \nabla C_- \quad (13)$$

Here no effort is made to differentiate the trapped anions from mobile anions. Instead, all the anions are assumed to be mobile. The anion concentrations is denoted as  $C_-$ . The other notations are the same as those in the TR-PNP model discussed above. In our calculation, the functional form of the ECP is simply assumed to be a step function, with constant nonzero value (adjustable parameter) inside the binding sites while zero elsewhere. It is found that smoothing of the discontinuity of the ECP term is not critical as the corresponding numerical results show very little change.

## 2.3 Parameter Estimation and Connections of the Two Methods

In this subsection, the methods of estimating the characteristic parameters (the total trap concentration  $N_T$ , the anion trapping coefficient  $c_-$  and the anion release coefficient  $e_-$ ) used in the TR-PNP model are discussed. In addition, we would like to present preliminary thoughts about the relation between the TR-PNP model and the ECP method.

The total trap concentration  $N_T$  (unit:  $\text{cm}^{-3}$ ) is the maximum number of trapped ions that one grid point

(actually its corresponding cubic cell in the 3-D mesh for the simulation) can accommodate. Let  $d_{ion}$  be the diameter of one single dehydrated ion, then  $N_T$  can be estimated roughly by

$$N_T = 1/d_{ion}^3 \quad (14)$$

The anion trapping coefficient  $c$  (unit:  $\text{cm}^3 \text{s}^{-1}$ ) is determined by the ion thermal velocity  $v_{th}$  and capture cross section  $\sigma$  as

$$c = v_{th} \sigma \quad (15)$$

A theoretical estimate for  $v_{th}$  by Einstein [11] assumes that  $v_{th}$  in condensed matter and in gases may be deduced in an analogous manner. From the kinetic theory,  $v_{th}$  can be estimated by

$$mv_{th}^2/2 = 3k_B T/2 \quad \text{or} \quad v_{th} = \sqrt{3k_B T/m} \quad (16)$$

where  $m$  is the particle mass,  $k_B$  the Boltzmann constant, and  $T$  the absolute temperature in Kelvin. Next, we assume that the effective capture cross section is equal to the area of one surface of the cubic cell in the mesh, that is,

$$\sigma = a^2 \quad (17)$$

where  $a$  denotes the side length of the cubic cell. Given Equation (15)-(17),  $c$  can be estimated.

As for the estimation of anion release coefficient  $e$  (unit:  $\text{s}^{-1}$ ), the Eyring rate theory [1] (sometimes called “transition state theory”) is invoked. The rate ( $k$ ) of ion crossing an energy barrier is written as

$$k = \nu \exp(-E_b/k_B T) \quad (18)$$

$$\nu = k_B T/h \quad (19)$$

where  $E_b$  is the barrier energy (the difference between the peak and the well of the free energy profile) and  $\nu$  a frequency prefactor  $6 \times 10^{12} \text{s}^{-1}$  for  $T = 300K$ .

In our approach, we propose that the ion release process can be characterized by Equation (18) and that the barrier energy therein is equivalent to the energy associated with the excess chemical potential  $\phi$ . Therefore, the ion release coefficient  $e$  can be estimated by

$$e = \nu \exp(-E_b/k_B T) = \nu \exp(-q\phi/k_B T) \quad (20)$$

These are the basic assumptions for relating the TR-PNP model to the ECP method.

In fact, one can show analytically that the ECP method represents a special case of our TR-PNP model and that they are indeed equivalent under some certain conditions. Those conditions are: first, the local chemical interaction is not too strong and the associated ECP value is less than  $6k_B T/q$ ; second, the system is in or close to steady state; third, we must have approximately

$$cN_T = \nu = k_B T/h \quad (21)$$

This equation gives, in our opinion, limitations to the models but does not necessarily have a physical basis.

### 3 RESULTS

We use PROPHET [12] as the computational platform for our simulations. The PROPHET simulator provides a user-friendly framework to solve systems of partial differential equations in 3-dimensional space as well as in the time domain.

Figure (1) shows the simulation volume given by a  $96\text{\AA} \times 96\text{\AA} \times 96\text{\AA}$  cubic box. A generic (toy) channel is immersed in an aqueous bath of potassium chloride (KCl) electrolyte solution. The channel pore connecting the left and right reservoirs is surrounded by protein (the shaded area). The lipid bilayer is neglected here for simplicity. The channel has a length of  $36\text{\AA}$  and a square cross section of  $6\text{\AA} \times 6\text{\AA}$ . Electrodes are immersed in the baths as left and right boundaries where Dirichlet boundary conditions are enforced for both the electrostatic potential and the ion concentrations. It is also required that the ion concentrations and electrostatic potential are continuous at the interfaces of the different regions.

In the steady-state simulation, a single anion binding site with a length of  $6\text{\AA}$  occupies the central part of the channel as shown in Figure (1). The fixed charge is distributed within a small  $3\text{\AA} \times 3\text{\AA} \times 3\text{\AA}$  volume in the middle of the protein wall. The charge density is assumed to be  $5 \times 10^{22}\text{cm}^{-3}$ . This particular model of binding site and charge distribution is to some extent arbitrary, however, may resemble the general characteristic of actual binding sites in real channels. The simulation results for the TR-PNP model and the ECP approach are shown in Figure (2) for comparison. The potential distribution along the axial direction of the channel under a bias voltage of  $150\text{ mV}$  is plotted at the top, and the current-voltage (I-V) characteristic curves at the bottom of this figure. The three sets of parameters used in the TR-PNP model and their corresponding ECP values are illustrated in Table 1. To be more specific,  $N_T$  is fixed at  $1 \times 10^{23}\text{cm}^{-3}$ , which is estimated by Equation (14).  $e_n$  is related to  $\phi$  by Equation (20). The only free adjustable parameter used in the simulation is  $c_n$ , whose values are obtained by fitting procedures and turn out to be of the same order of magnitude as estimated from Equation (15). Furthermore, it is shown that provided the conditions given at the end of the previous section (Equation (21) satisfied within a factor of 2) the two approaches are indeed equivalent by leading to virtually identical numerical results.

The TR-PNP model can in addition deal with time dependencies. For the implementation of transient simulations, another toy channel with similar geometry has been investigated. It has now two binding sites located symmetrically inside the channel pore, as shown in Figure (3). Both binding sites have modelling parameters identical to the single binding site of the previous structure. In Figure (4), the transient simulation result for a

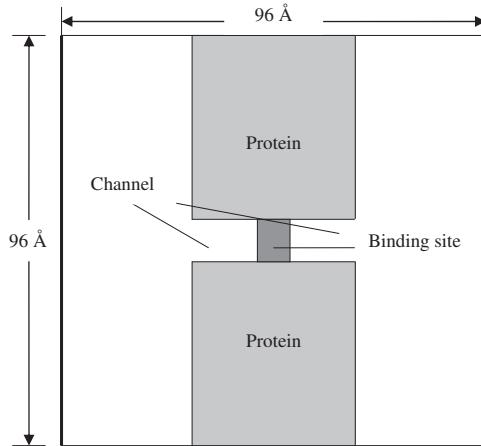


Figure 1: Schematic plot of a toy anion-selective channel with single binding site

period of  $1\mu\text{s}$  is presented by showing how the anion concentration distribution profile evolves with time for six different time steps. The majority of anions move from the left binding site to the right within about  $0.5\text{ns}$ , producing large currents over a short distance in this short period of time. This simulation outcome can be interpreted as an indicator of individual ion hopping processes. In order to verify this, we have integrated the numerical values of the currents at different time steps and the result turns out to be approximately equal to one elementary charge.

### 4 CONCLUSION

We have used two different methodologies, the TR-PNP model and the ECP method to simulated some generic ion channel structures. Their relations have been discussed and they are equivalent under certain conditions particularly in steady state. The TR-PNP model is more general as it can handle transient simulations over long timescales and describes to some extent particle properties within the continuum model framework. Therefore this method is a promising candidate for a multi-scale simulation hierarchy.

### ACKNOWLEDGEMENT

This material is based upon work supported by the National Science Foundation under Grant No. EEC-0228390. We are grateful to Professor Robert Dutton and his group for introducing us to Prophet, Dr. Robert Eisenberg, Dr. Eric Jakobsson and Dr. Trudy van der Straaten for many valuable discussions.

Table 1: Parameters used in the TR-PNP model and the ECP approach

Parameter Set	$\phi = \text{ECP}$ (mV)	$e_- = \nu \exp(-q\phi/k_B T) (\text{s}^{-1})$	$c_- (\text{cm}^3 \text{s}^{-1})$	$N_T (\text{cm}^{-3})$
1	50	$9.01 \times 10^{11}$	$7.60 \times 10^{-11}$	$1 \times 10^{23}$
2	100	$1.30 \times 10^{11}$	$6.05 \times 10^{-11}$	$1 \times 10^{23}$
3	150	$1.88 \times 10^{10}$	$3.20 \times 10^{-11}$	$1 \times 10^{23}$

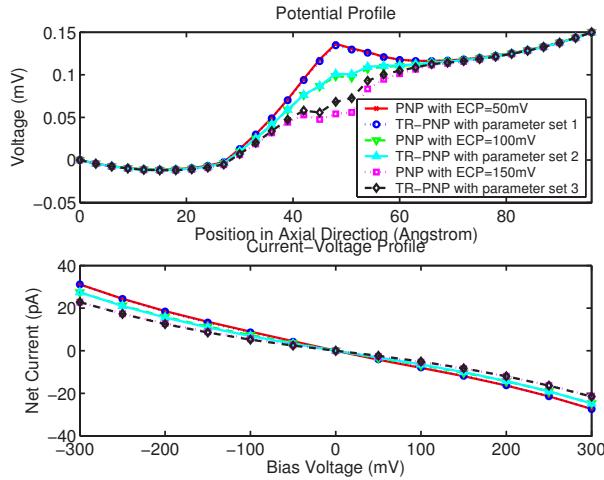


Figure 2: Comparison of simulation results for both the TR-PNP and ECP method

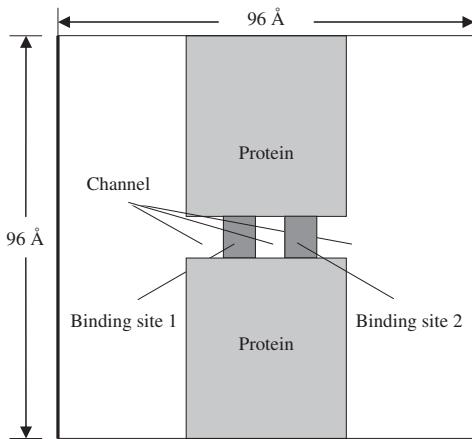


Figure 3: Schematic plot of another toy anion-selective channel with two binding site

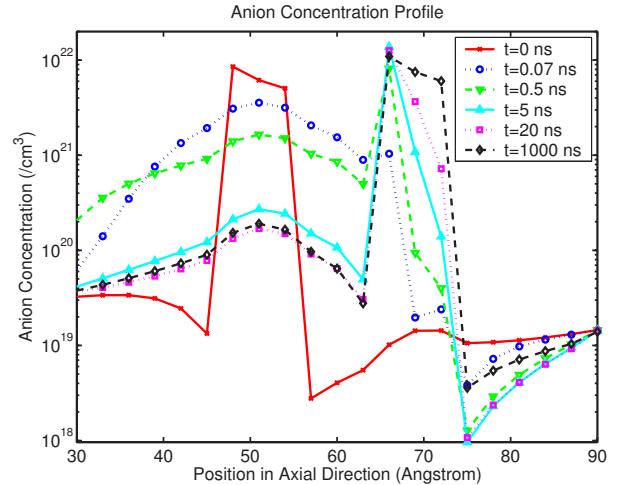


Figure 4: Transient process in an anion channel. The majority of ions move from the left binding site to the right one producing large currents within 0.5ns, thus illustrating the ion hopping process

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