Ion Trapping and Release Using Computational Electronics Methods

Sai Hu and Karl Hess
Beckman Institute and Department of Electrical and Computer Engineering
University of Illinois at Urbana-Champaign
405 N. Mathews Ave., Urbana, IL 61801, USA

Abstract: An extension (TR-PNP) of the traditional PNP model is proposed to explicitly taking into account the effects of ion trapping and release. Our approach to this problem has originated from the treatment introduced by Shockley, Read and Hall model in semiconductor theory. The ion release rate is related to the calculated excess chemical potential (ECP) through the Erying's rate theory. Simulation results are presented for the Gramicidin A channel by using the traditional PNP model, the PNP-ECP model and the TR-PNP-ECP model and are compared with experiments.

Key-Words: Biological Ion Channel, Poisson-Nernst-Planck (PNP) Model, TR-PNP Model, Shockley-Read-Hall (SRH), Excess Chemical Potential (ECP)

1   Introduction

Ion channels [1] are biological nanotubes formed by membrane proteins. Each channel consists of one or more chains of amino acids folded in such a way that a nanoscopic water-filled pore is produced. One essential function of the ion channels is to regulate the flow of ions into and out of cells. Many electrical activities of cells and tissues are produced by the controlled movement of charged species. In addition, Ion channels can selectively transmit or block particular types of ions very effectively and efficiently. Some of them exhibit gating properties which are very similar to the switching functions of electronic devices. Their fundamental importance to biological functions and device-like features are appealing to both biophysicists and electrical engineers for the prospects of their novel applications in the area of nanotechnology and biomedical engineering.

In the past decade, there have been enormous strides in our understanding of structure-function relationships for biological ion channels. This advance has been achieved by the combined efforts of experimental and computational studies. In recent experimental breakthroughs, the crystal structures of several natural channels have been determined from the X-ray crystallographic analysis with resolutions of a few angstroms [2]. Parallel to these landmark findings, great progress has also been made in the computational endeavors. The methods that are employed, from fundamental to phenomenological, are molecular dynamics (MD), Brownian dynamics (BD), Monte-Carlo (MC) methods and continuum models of electro-diffusion [3]. Each of these approaches has advantages and drawbacks and is capable of providing useful information about the ion transport mechanisms in channels.

One common objective is to find a reasonable and tractable modeling and simulation hierarchy which is able to cover as many molecular details as possible while achieving computational efficiency and robustness. In this paper, we present a novel method (the TR-PNP model) which can deal with some microscopic properties (the ion trapping and release effects) within the traditional continuum framework. The original idea comes from the Shockley-Read-Hall (SRH) model widely used in semiconductor device simulations.

2   Models

In this section, one commonly used continuum model, the Poisson-Nernst-Planck (PNP) model, is first introduced briefly and the motivation of improving this model is explained from the perspective of the ion trapping and releasing effects. The TR-PNP model is then proposed to account for these important effects. Subsequently issues regarding the parameter estimation are discussed, some of which are related to the traditional transitional state theory and the excess chemical potential approach.

2.1   The PNP Model

Continuum theories of electrolytes, such as the Poisson-Boltzmann (PB) equations and the Poisson-Nernst-Planck (PNP) equations, have been used in the studies of biological ion channels. The PB theory is limited to the electrostatic study of equilibrium states. The PNP theory has been utilized to investigate the permeation and transport properties

of many ion channels [4][5]. The underlying physics is nothing but the coupled system of Poisson equation and the drift-diffusion equation. One impressive advantage of this theory is its capacity to describe the fundamental mechanism of ion transport with relatively low computational demands. The PNP method has achieved some level of success in predicting some macroscopic characteristics such as current-voltage profiles (I-V curves). The agreement with experimental data is reasonably good especially if some key parameters used in the model are freely adjusted.

Nevertheless, continuum models view individual ions as diffusive charge clouds represented only by concentration densities. Thus properties specific to the discrete particle nature cannot be covered by this method. For example, the ion trapping and release effects are extremely difficult to be addressed within the traditional PNP model.

2.2 The TR-PNP Model

From a theoretical point of view, the equations used in the PNP model are not as complete as those used for semiconductors because they neglect the generation and recombination terms [6][7]. In semiconductors, these terms describe the interactions of carriers with crystal imperfection sites or generation-recombination centers, known as the capture and emission of carriers [6]. Biological ion channels do not have the exact counterparts to those centers. However, chemical bonding or other types of localization effects of the ions in certain regions of the channel proteins are an essential part of the conduction and switching mechanism of ion channels. In other words, ions can be trapped into and released from the so-called binding sites where strong interactions between the ions and the channel environment occur. In fact, ion trapping and release effects have been demonstrated both theoretically and experimentally to be crucial for a large variety of natural ion channels, such as the KcsA potassium channel [8][9] and the ClC chloride channel [10][11].

2.1.1 Analogy to the SRH Model

The above discussion indicates an analogy between the carrier-crystal interactions at imperfection sites in semiconductors and the ion-protein interactions at binding sites in ion channels. This suggests using terms that are analogous to the Shockley-Read-Hall (SRH) generation and recombination expressions [6] used in the semiconductor theory to describe the trapping and release process of ions. The conventional PNP theory is thus extended to the more general TR-PNP model by incorporating the ion trapping and release effects. Our new method [7][12]

therefore creates a bridge connecting macroscopic continuum models and microscopic particle properties.

2.2.2 Formulation of the TR-PNP model

In general, each particular binding site is specific to either positive ions (in cation-selective channels) or negative ions (in anion-selective channels). In the following, a model is given describing the binding sites for cations only. It is straightforward to supplement it to accommodate anion binding sites or even both types of binding sites.

$$\nabla \bullet (\varepsilon \nabla \varphi) = q(C_+^m - C_+^t - C_- + C_{fixed}) \qquad (1)$$

$$\frac{\partial C_-}{\partial t} + \nabla \bullet \vec{F}_- = G_- = 0 \qquad (2)$$

$$\frac{\partial C_+^m}{\partial t} + \nabla \bullet \vec{F}_+ = G_+^m = -c_+ C_+^m (N_{T+} - C_+^t) + e_+ C_+^t \qquad (3)$$

$$\frac{\partial C_+^t}{\partial t} = G_+^t = +c_+ C_+^m (N_{T+} - C_+^t) - e_+ C_+^t \qquad (4)$$

$$\vec{F}_+ = -\mu_+ C_+ \nabla \varphi - D_+ \nabla C_+^m \qquad (5)$$

$$\vec{F}_- = +\mu_- C_- \nabla \varphi - D_- \nabla C_- \qquad (6)$$

where φ denotes the electrostatic potential, ε the dielectric constant, q the absolute value of the elementary charge, and C_{fixed} the fixed charge on the protein wall. One distinction from the conventional PNP model is that the trapped cations are explicitly differentiated from the mobile ones and their concentrations are expressed as C_+^t and C_+^m, respectively. The anions are all mobile since no anion binding is considered in the present model. Their concentration is expressed as C_-. In addition, three characteristic parameters are used to describe the cation trapping and release processes through the generation and recombination terms in the continuity equation. They are the cation trapping coefficient c_+, the cation release coefficient e_+ and the total cation trap density N_{T+}. They have non-zero values in the binding site regions and zero values everywhere else.

We refer to the above model and system of equations Eq. (1)-(6) by the acronym TR-PNP where "TR" denotes the inclusion of ion trap and release effects.

For the case of anion binding, it can be dealt with by introducing another set of three characteristic

parameters and making the distinction of mobile and trapped anions. All the equations remain very similar.

2.2.3 Parameter Estimation

The major question when using the TR-PNP model is, of course, how to obtain the numerical values for the characteristic parameters. The estimation methods with some simplifying assumptions are given as follows.

The total trap concentration N_{T+} (unit: cm^{-3}) is the maximum number of trapped ions that one grid point (actually its corresponding cubic cell in the three-dimensional mesh of the simulation system) can accommodate. From the scenario of closely packed ions, it is essentially related to the diameter of one single dehydrated ion d_{ion}. Thus N_{T+} can be approximated by

$$N_{T+} = \frac{1}{d_{ion}} \qquad (7)$$

The anion trapping coefficient c_+ (unit: cm^{3}s^{-1}) can be determined by the product of ion thermal velocity v_{th} and capture cross section σ. A theoretical estimate for v_{th} can be calculated from the kinetic theory based on the assumption that v_{th} in condensed matter and in gases may be deduced in an analogous manner. Next, we assume that the effective capture cross section is equal to the area of one surface of the cubic cell in the mesh. Therefore, we may estimate c_+ by:

$$c_+ = \sigma v_{th} = a^2 \sqrt{\frac{3k_B T}{2m}} \qquad (8)$$

where m is the mass of the ion and a the mesh size.

As for the estimation of anion release coefficient e_+ (unit: s^{-1}), the Eyring rate theory [1] (sometimes called "transition state theory") is invoked. The rate of ion crossing an energy barrier is given by

$$e_+ = \upsilon \exp(-\frac{E_b}{k_B T}) = \frac{k_B T}{h} \exp(-\frac{E_b}{k_B T}) \qquad (9)$$

where E_b is the barrier energy (the difference between the peak and the well of the free energy profile) and υ a frequency prefactor which is equivalent to the energy of one $k_B T$.

2.2.4 Excess Chemical Potential

As seen from the above, the estimation method for release coefficient is much more sophisticated. Precise and accurate definitions of the barrier energy as well as the pre-factor used in the Eyring rate theory

have not been well established yet and are still under investigation. In our approach, we use the hypothesis that the barrier energy E_b is equivalent to the excess chemical potential (ECP). In our previous work [12], we have used this hypothesis to study a model channel with uniform ECP inside the binding sites. We have shown the TR-PNP model is virtually equivalent to the ECP correction model both numerically and theoretically under some certain conditions. Nevertheless, that example is too simplistic in the treatment of ECP profile as well as the channel structure. In the present work, we want to explore the relations of the TR-PNP model and the ECP terms by relying on more complex approaches to obtaining the ECP profile for realistic channels.

One viable approach to calculate the excess chemical potential has been proposed and utilized in simulating ion channels. It is carried out by use of the density functional theory (DFT) [13]. The free energy of the near equilibrium system is required to be minimum, which introduces an extra correction term, the ECP term. The ECP correction has two contributions, one from the finite size effect of the ions and water molecules, the other from the non-singular charge distribution of the ions. The ECP correction terms for ions and water molecules can then be inserted into the conventional PNP model to form the self-consistent PNP-ECP model [14].

Based on the calculated ECP terms and the hypothesis that the ECP terms can be used in the Eyring rate equation, one is able to calculate the ion release rate and then use it for the TR-PNP model. Consequently, a combination of the TR-PNP model and the ECP profile is formed which extends the pure PNP-ECP model that does not take into account the ion trapping and release explicitly.

In the next section, we describe the simulations by using three different models, the conventional PNP model, the PNP-ECP model and the TR-PNP-ECP model.

3 Simulations and Results

3.1 Simulator: PROPHET

The PROPHET simulator provides a user-friendly framework to solve systems of partial differential equations in one, two or three dimensions of space as well as in the time domain. The PDE's are discretized using either finite elements or finite volume methods in space and implicit methods in time, reducing the differential equations to a large system of algebraic equations. The algebraic equations are solved by

Newton's method. The matrix resulting from the linearization is solved by sparse iterative or direct methods. It also has the capability of handling arbitrary geometries such as those encountered in biological system. The discretization library makes no assumptions about the domain but uses arbitrary combinations of elements to describe its shape, such as triangles and quadrilaterals in 2D, tetrahedra, bricks or prisms in 3D. There are limited built-in grid generation facilities. However, arbitrary grids can be read from external sources and calculations can be performed on those domains. Furthermore, it provides the users not only with the flexibility to construct different types of differential equations by using a large variety of prefabricated physical operators and geometrical operators, but also the freedom to add new types of operators and equations according to specifications. All the relevant coefficients, as well as the calculation control parameters, are stored in a library. Physical properties such as dielectric constants and diffusion coefficients can be easily specified by accessing the library. In all, PROPHET provides a convenient scripting framework enabling us to define, discretize and solve an arbitrary system of partial differential equations. Originally it was developed for semiconductor simulations. However, it has been shown to be beneficial to take advantage of this well developed numerical tool in the new arena of ion channel simulations [5][7][12], which is also the theme of the present work.

3.2 The Gramicidin A (GA) Channel
The Gramicidin A (GA) channel is an antibiotic polypeptide that consists of 15 amino acid residuals. It is approximately 24Å in length and 4Å in diameter. It selectively conducts monovalent cations, binds divalent cations and completely blocks all anions. Because of its relatively small and simple structure and the ease with which it can be synthesized, gramicidin has been well studied both experimentally and theoretically. High-resolution structures of the GA channel have been determined from the solution NMR and solid-state NMR experiments. Efforts in theoretical studies have evolved from simple electrostatic calculations with rigid dielectric boundaries to sophisticated MD simulations with GA embedded in a lipid bilayer and solvated with water. Most of the free-energy profiles of ions obtained from these studies are in qualitative agreement with the observed binding sites at each end of the channel and a central barrier in between them. Recent NMR study of cation transport in the channel has shed more light on this problem by demonstrating that the GA peptide remains rigid upon cation binding and the ion

is solvated by two carbonyl oxygens [15]. All these findings suggest the application of the TR-PNP model, which is able to treat the ion binding effects explicitly, in examining this particular channel.

3.3 Simulation Issues and Methods
The molecular structure of the GA channel is obtained from the Protein Data Bank with the ID number: 1MAG. The original PDB file is transformed into the PQR file with atom radii and charge information added [16]. Then BioMOCA [17] is used to generate the material map. In the next step, based on the PQR file and the material map file, the charge distribution file and the mesh file are produced. A $46\times46\times100$ grid with a grid spacing of 0.5Å is used. The schematic plot of the simulation system is shown in Fig. 1. The GA channel is immersed in between the left bath and right bath region filled with the electrolyte (such as NaCl or KCl) solution with a concentration of 1M/L. The bias voltage can be applied to one boundary with the other one grounded. In consequence, ions will flow through the channel pore. The main objective of theoretical studies is to predict the current-voltage (I-V) relations.
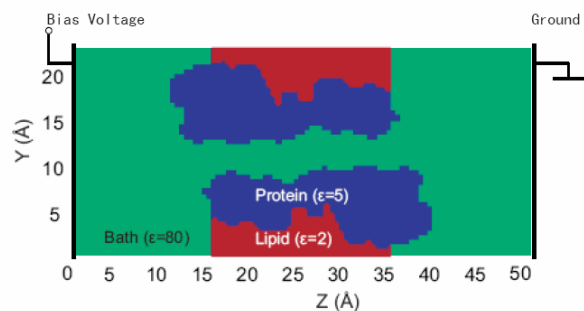

Figure1: Schematic plots of the simulation system involving the Gramicidin A channel.

As mentioned in the above subsection, the two binding sites in the GA channel play an important role in the cation selectivity and conduction mechanism. The self-consistent PNP-ECP model has been used already to calculate the ECP correction and successfully demonstrated the binding sites quantitatively in terms of the ECP profiles [14]. The numerical values of ECP inside the binding regions can be substituted into Eq. (9) to compute the corresponding space-dependent cation release coefficients. The cation trapping coefficients and total cation trap concentration can be estimated through the methods given in Section 2.2.3. The values are dependent on the mass and diameter of each particular type of ions. In consequence, the

TR-PNP calculations can also be carried out to predict the I-V curves.

3.4 Results

In the following, the results of sodium ion and potassium ion transport through the GA channel are given in Fig. 2 and Fig. 3 respectively. The experimental data from [18] is also plot for comparison. Three different methods are used for the calculations, the conventional PNP model, the PNP-ECP model and the TR-PNP-ECP model. In all the models, no fitting parameters are used. The dielectric constants used for the protein, lipid and electrolyte region are shown in Fig. 1. Moreover, the ion diffusion constants and mobilities are assumed to maintain their values in the bulk and have a uniform distribution.

As seen from the two figures, the TR-PNP-ECP model achieves a much better agreement with the measurements than both the PNP model and the PNP-ECP model. It works surprisingly well for two different types of ions, both the sodium ions and the potassium ions, especially with no freely adjustable parameters present. Our approach of estimating the characteristic parameters with the ECP correction as inputs can therefore be justified. Furthermore, these results demonstrate that the TR-PNP-ECP model is capable of dealing with ion specific properties.

One may wonder why the PNP-ECP model itself cannot produce satisfactory results while the ECP profiles turn out to be meaningful inputs to the TR-PNP model. In our point of view, the fundamental reason is that the PNP-ECP model does not differentiate between trapped ions and mobile ions. In contrast, the TR-PNP model makes this distinction explicit and describes their dynamic exchange processes by referring to the SRH model. Covering the ion trapping and release effects must be the key to studying the binding sites and their roles in ion transport through the channels.

On the other hand, the PNP-ECP model achieves some degree of success in the sense that it provides a self-consistent way to calculate the ECP. The TR-PNP model, however, can further improve the predictions with important particle properties of the ions taken into account to some extent.

In addition, the TR-PNP model can deal with time-dependent problems as well, even for time periods much longer than molecular dynamics can handle. Some preliminary results can be found in [7][12].
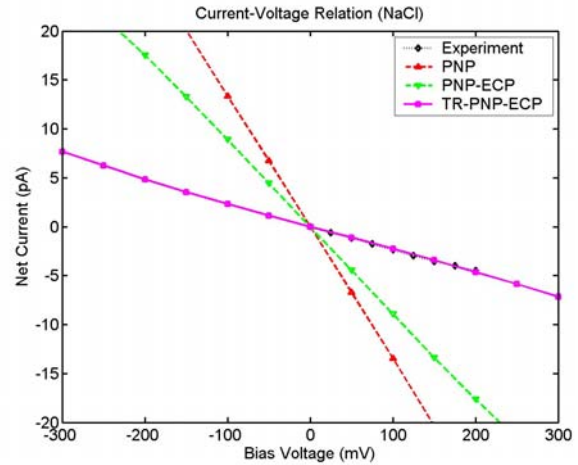

Figure 2: I-V relations of the GA channel immersed in the NaCl solution (1M/L).
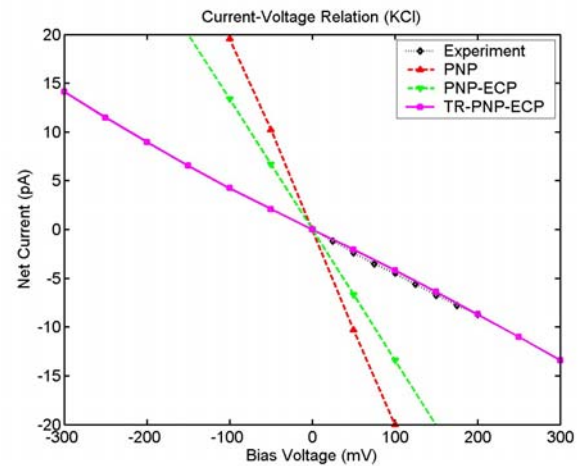

Figure 3: I-V relations of the GA channel immersed in the KCl solution (1M/L)

4 Conclusion

In this paper, the importance of the ion trapping and release effects in ion channels has been explained. The TR-PNP model has been proposed to address these effects. We have shown that when it is used together with the self-consistent ECP results, the predicted I-V curves are entirely consistent with the experimental data. Further improvement can possibly be achieved by coupling the model with the MD or MC simulations and then finding better estimates for the characteristic parameters.

In all, the TR-PNP model is capable of accounting for some particle properties in the framework of non-equilibrium continuum models. It provides a bridge connecting the microscopic and macroscopic models and simulation methodologies. It is a promising candidate to being integrated into a multi-scale simulation hierarchy.

Acknowledgement

References:

[1] B. Hille, *Ionic Channels of excitable Membranes*, 2nd Ed., Sinauer Associate Inc., Sunderland, MA, 1992

[2] D. A. Doyle, et al., The structure of the potassium channel: molecular basis of K^+ conduction and selectivity, *Science*. Vol. 280, 1998, pp. 69-77.

[3] B. Roux, T. Allen, S. Berneche and W. Im, Theoretical and computational models of biological ion channels, *Quarterly Reviews of Biophysic*, Vol. 37, 2004, pp. 15-103.

[4] R. S. Eisenberg, From structure to function in open ionic channels, *J. Membr. Biol.* Vol. 171, 1999, pp. 1-24.

[5] T. A. van der Straaten, J. M. Tang, U. Ravaioli, R. S. Eisenberg, N. R. Aluru, *Simulating ion permeation through the ompF porin ion channel using three-dimensional drift-diffusion theory*, *J. Comp. Elec.* Vol. 2, 2003, pp. 29-47.

[6] K. Hess, *Advanced Theory of Semiconductor Devices*, IEEE Press, New York, 2000

[7] S. Hu and K. Hess, An Application of the Recombination and Generation Theory by Shockley, Read and Hall to Biological Ion Channels, *J. Comp. Elec.*, Vol. 4, 2005, pp. 153-156.

[8] Y. Zhou, J. H. Morais-Cabral, A. Kaufman, and R. MacKinnon, Chemistry of ion coordination and hydration revealed by a K^+ channel – Fab complex at 2.0 Å resoluation, *Nature*. Vol. 414, 2001, pp. 43-48.

[9] S. Berneche and B. Roux, Energetics of ion conduction throught the K^+ channel, *Nature*. Vol. 414, 2001, pp. 73-77.

[10] R. Dutzler, E. Campbell and R. MacKinnon, Gating the selectivity filter in ClC chloride channels, *Science*, Vol. 300, 2003, pp. 108-112

[11] D. Bostick and M. Berkowitz, Exterior site occupancy infers chloride-induced proton gating in a prokaryotic homolog of ClC chloride channel, *Biophys. J.*, Vol. 87, 2004, pp. 1686-1696.

[12] S. Hu and K. Hess, Ion Channel Simulations Using the TR-PNP Model and the Excess Chemical Potential Approach, in The Technical Proceedings of 2005 NSTI Nanotechnology Conference and Trade Show, presented at the 5th International Conference of Computational Nanoscience and Nanotechnology, Anaheim, CA, May 8-12, 2005.

[13] Y. Rosenfeld. Free energy model for inhomogeneous fluid mixtures: Yukawa-charged hard spheres, general interactions, and plasmas. *Journal of Chemical Physics*, Vol. 98, No. 10, 1993, pp. 8126–8148.

[14] Private communications with Z. Yang and Professor U. Ravaioli at University of Illinois

[15] F. Tian and T. A. Cross, Cation transport: an example of structural based selectivity, *J. Mol. Biol. Vol. 285*, 1999, pp. 1993-2003.

[16] N. A. Baker, D. Sept, S. Joseph, M. J. Holst, J. A. McCammon, Electrostatics of nanosystems: application to microtubules and the ribosome, *Proc. Natl. Acad. Sci. USA*, Vol. 98, 2001, pp. 10037-10041.

[17] T. A. van der Straaten, G. Kathawala, A. Trellakis, R. S. Eisenberg, and U. Ravaioli, Biomoca: a boltzmann transport monte carlo model for ion channel simulation, *Molecular Simulation*, Vol. 31, 2005, pp.151-171.

[18] D. Busath, et. al., Noncontact Dipole Effects on Channel Permeation. I. Experiments with (5F-Indole) Trp13 Gramicidin A Channels, *Biophys. J.*, Vol. 75, 1998, pp. 2830-2844.