

Ionic Diffusion Through Protein Channels: From Molecular Description to Continuum Equations

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ABSTRACT

Ionic permeation through protein channels is a process of considerable physiological importance. Permeation occurs on a microsecond time scale, so direct molecular simulations with femtosecond time increments are not possible and a coarser description is unavoidable. Standard continuum formulations based on macroscopic conservation laws, such as the Poisson-Nernst-Planck equations, however, cannot be assumed valid in narrow channels. Thus the problem at hand is the description of ionic diffusion through narrow regions by averaged continuum equations. In this paper we propose a mathematical averaging procedure that, starting from a Langevin model of ionic motion, yields a coupled system of Poisson and Nernst-Planck type equations, containing conditional and unconditional charge densities. The proposed system of equations includes molecular details such as excluded volume effects and the dielectric force on a discrete ion that are absent in the PNP system.

Keywords: Ion Channels, Brownian motion, Non Equilibrium Statistical Physics

1 INTRODUCTION

Protein channels embedded in biological membranes are natural nano-devices of considerable physiological importance [1]. Ionic permeation through protein channels occurs on a microsecond time scale, so direct molecular simulations of the permeation process with femtosecond time increments are not possible and a coarser description is unavoidable [2].

One of the common coarse grained descriptions of ion channels is based on the Poisson-Nernst-Planck (PNP) system [3], [4]. This system of equations, commonly used in plasma physics and semiconductor device modelling, is based on macroscopic conservation laws. While macroscopic conservation laws clearly govern the macroscopic behavior of ensembles of channels, their application to a single protein channel that can contain at most one or two ions at a time is questionable [5].

One of the key missing elements in PNP is its derivation from a molecular model. In this paper we present a molecular model of permeation, based on diffusive motion of ions, and propose a mathematical averaging pro-

cedure that results in a hierarchy of Poisson and Nernst-Planck type equations containing conditional and unconditional charge densities. The proposed *conditional* system, denoted C-PNP, includes molecular details such as excluded volume effects and the dielectric force on a discrete ion that are absent in the standard PNP system. The C-PNP system, along with a closure relation and boundary conditions thus enables the theoretical study of non-equilibrium diffusing systems. Its application to ion channels can predict blocking and possibly selectivity.

2 FORMULATION

We consider a finite system composed of two macroscopic volumes connected by one or more protein channels. The system, containing a solution of different species of diffusing interacting ions, is driven out of equilibrium by a connection to a feedback mechanism that keeps different average concentrations in the two volumes (see fig. 1). The feedback mechanism, located only on parts of the system boundaries, senses the concentrations at these boundaries and removes or injects ions instantly so as to maintain average fixed concentrations there at all times.

The problem at hand is to deduce the function of the channel given its structure, that is, to describe the dependence of the steady diffusion current flowing between the two baths as a function of the geometry and charge distribution of the channel, the molecular properties of the diffusing ions (their radii and interaction forces), and as a function of the experimentally controlled variables, such as bath concentrations and the external potential.

We introduce the following notation. The finite domain, that consists of the two macroscopic volumes and the connecting channel, is denoted Ω . Its boundary $\partial\Omega$ is composed of reflecting boundaries $\partial\Omega_R$ and the feedback boundaries $\partial\Omega_F$. We assume that there are N^h ions of species h ($h = Ca^{++}, Na^+, Cl^-, \dots$) in Ω , which are numbered at time $t = 0$, $\sum_h N^h = N$, and we follow their trajectories at all times $t > 0$. The coordinates of a point are denoted by $\mathbf{x} = (x, y, z)$, while the location and velocity coordinates of the j -th ion of species h at time t are denoted by $\mathbf{x}_j^h(t)$ and $\mathbf{v}_j^h(t)$, respectively. According to our assumptions, an ion that reaches $\partial\Omega_F$ is

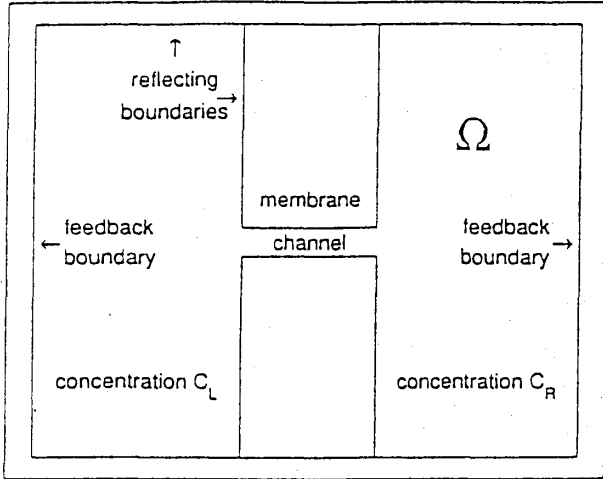


Figure 1: The region Ω

instantly re-injected by the feedback mechanism at one or another part of the boundary, so that its individual identity is preserved, and consequently the total number of ions inside Ω is fixed at all times.

2.1 Equations of motion

Under physiological conditions, ionic solutions contain many more solvent water molecules than solute diffusing ions. Thus, the collective motion of only the ions (without the water) is a lower dimensional projection of the joint motion of all water and ion molecules in the solution. Since the motion of ions in solution is strongly overdamped, on time scales larger than the relaxation time of the solution, memory effects due to the thermal motion of the solvent can be neglected [6]. Thus, the joint motion of only the ions can be described by the following memoryless system of coupled Langevin equations for the different ion species $h = Ca^{++}, Na^+, Cl^-$, etc., $j = 1, \dots, N^h$,

$$\ddot{x}_j^h + \gamma^h(x_j^h) \dot{x}_j^h = \frac{f_j^h}{M^h} + \sqrt{2\varepsilon^h \gamma^h(x_j^h)} \dot{w}_j^h, \quad (1)$$

where a dot on a variable denotes differentiation with respect to time, $\gamma^h(x^h)$ is the location dependent friction coefficient per unit mass, M^h is the effective mass of an ion of species h , $\varepsilon^h = k_B T / M^h$, k_B is Boltzmann's constant and T is absolute temperature. The force on the j -th ion of species h , denoted f_j^h , includes all ion-ion interactions and thus depends on the locations of all ions. The functions \dot{w}_j^h are, by assumption, independent standard Gaussian white noises.

2.2 The Fokker-Planck Equation

We define by $p_N(x_1, \dots, x_N, v_1, \dots, v_N)$ the stationary probability density function (pdf) of the system of all N ions. Since the coupled motion of all ions is

governed by the Langevin system (1) with independent noise terms, the stationary pdf p_N satisfies the multi-dimensional stationary Fokker-Planck equation [7]

$$0 = \sum_h \sum_{j=1}^{N^h} \mathcal{L}_j^h p_N, \quad (2)$$

where \mathcal{L}_j^h is the Fokker-Planck operator acting on the phase space coordinates of the j -th ion of species h . It is given by

$$\begin{aligned} \mathcal{L}_j^h p_N &= \nabla_{v_j^h} \cdot \left(\gamma^h(x_j^h) v_j^h - \frac{f_j^h}{M^h} \right) p_N \\ &+ \Delta_{v_j^h} \varepsilon^h \gamma^h(x_j^h) p_N - v_j^h \cdot \nabla_{x_j^h} p_N, \end{aligned}$$

where the operators ∇_v and Δ_v denote the gradient and the Laplacian with respect to the variable v , respectively. Equation (2) is defined in the $3N$ dimensional region $(x_1, \dots, x_N) \in \Omega^N$ and $(v_1, \dots, v_N) \in R^{3N}$.

3 THE C-PNP SYSTEM

3.1 Concentrations and Probability Densities

We denote by $c^h(x)$ the time-averaged steady state concentration of ions of species h at location x , and by $p_j^h(x)$, $j = 1, \dots, N^h$, the stationary probability density function of the location of the j -th ion of species h . By definition, the pdf of a single particle is simply the marginal density of all particles integrated over all particle locations except the j -th ion of species h ,

$$p_j^h(x_j^h) = \int_{\Omega^{N-1} \times R^{3N}} p_N d\bar{x}_j^h dv_1 \dots dv_N \quad (3)$$

where \bar{x}_j^h is the vector of all $N - 1$ particle coordinates except x_j^h .

Since all ions of a given species are indistinguishable, $p_j^h(x) = p^h(x)$, for all j . The quantities $c^h(x)$ and $p^h(x)$ are thus related by

$$c^h(x) = N^h p^h(x). \quad (4)$$

The concentration $c^h(x)$ is the physical density of ions and it integrates to the total number of ions of species h in the solution. An equation for $p^h(x)$ readily turns into an equation for $c^h(x)$ by the relation (4).

Starting from the Langevin model (1), by integrating the full Fokker-Planck equation (2) over all coordinates but one, the following Nernst-Planck type equation for the concentration $c^h(x)$ was derived in [5],

$$0 = -\nabla_x \cdot J^h(x), \quad (5)$$

where $J^h(x)$ is the flux density of type h ions, given by

$$J^h(x) = \frac{\bar{f}^h(x)}{M^h \gamma^h(x)} c^h(x) - \frac{\varepsilon^h}{\gamma^h(x)} \nabla_x c^h(x). \quad (6)$$

The quantity $\bar{f}^h(x)$ in (6) is the average force on a single ion of type h . It is given by

$$\bar{f}^h(x) = \int_{\Omega} \int_{\Omega^{N-1}} f_j^h p_{N-1}(\bar{x}_j^h | x_j^h = x) d\bar{x}_j^h, \quad (7)$$

where $p_{N-1}(\bar{x}_j^h | x_j^h = x)$ is the conditional probability density of the $N-1$ remaining ions given a type h ion located at x .

In the case of charged ions in solution, the ion-ion interaction forces are pair-wise additive, and thus the force on the j -th ion of species h can be written as

$$f_j^h = f_{ed}^h(x_j^h) + \sum_{(i,h') \neq (j,h)} f^{h,h'}(x_i^{h'}, x_j^h), \quad (8)$$

where $f^{h,h'}$ is the ion-ion interaction force that an ion of type h' acts on an ion of type h . It includes both Coulombic interactions as well as short range interactions, such as excluded volume or Lennard-Jones forces. The force f_{ed}^h contains both the effects of an applied external field as well as the dielectric self-force near dielectric boundaries [5], [8].

As shown in [5], with the specific form (8) for the force on a single ion, equation (7) for the average force simplifies to

$$\bar{f}^h(x) = f_{ed}^h(x) + \bar{f}_{SR}^h(x) - z^h e \nabla_y \bar{\phi}^h(y|x) \Big|_{y=x}$$

where

$$\bar{f}_{SR}^h(x) = \sum_{h'} \int_{\Omega} f_{SR}^{h,h'}(y,x) c^{h'|h}(y|x) dy, \quad (9)$$

is the average short range force on a type h ion, z^h is the valence of type h ions and $\bar{\phi}^h(y|x)$ is the conditional electrostatic potential at y given a type h ion at x . It satisfies the (conditional) Poisson equation

$$\nabla_y \cdot \varepsilon(y) \nabla_y \bar{\phi}^h(y|x) = -e \sum_{h'} z^{h'} c^{h'|h}(y|x), \quad (10)$$

where $\varepsilon(y)$ is the dielectric coefficient at y . In both eq. (9) and (10), $c^{h'|h}(y,x)$ is the conditional concentration of h' ions at y given an h -type ion at x . In terms of unconditional quantities, it is given by

$$c^{h'|h}(y|x) = \frac{c^{h,h'}(x,y)}{c^h(x)}. \quad (11)$$

To summarize, the density $c^h(x)$ satisfies a Nernst-Planck type equation (5), with an average force \bar{f}^h that

is the sum of a dielectric self force, an averaged short range force (9) and an averaged electrostatic force. The latter is a solution of a conditional Poisson equation that depends on conditional densities, in contrast to the unconditional densities in the standard PNP formulation. We denote this resulting system of conditional Poisson and Nernst-Planck equations by C-PNP.

The NP equation (5) is defined in the finite domain Ω . Therefore, in addition to the determination of the averaged force \bar{f}^h , boundary conditions on $\partial\Omega$ must be specified in order to determine the unique solution for $c^h(x)$. Obviously, on $\partial\Omega_R$, $c^h(x)$ satisfies no flux boundary conditions,

$$J^h(x) \cdot \nu \Big|_{x \in \partial\Omega_R} = 0. \quad (12)$$

In addition, on $\partial\Omega_F$, according to our assumptions, the concentrations $c^h(x)$ are maintained at fixed known values $c_F^h(x)$ by the feedback mechanism. Therefore, regardless of the exact method by which the feedback mechanism maintains these concentrations,

$$c^h(x) = c_F^h(x), \quad \text{for } x \in \partial\Omega_F. \quad (13)$$

3.2 The C-PNP Hierarchy

An important difference from the PNP system is that the C-PNP system is not closed. As seen from (9) and (10), the averaged force in the Nernst-Planck equation (5) depends on conditional higher order concentrations. Thus, we now write an equation for the pair concentrations. Employing similar methods to those of [5], we obtain that $c^{h,h'}(x,y)$ satisfies the following equation

$$\nabla_{x^h} \cdot J_{x^h}^{h,h'}(x,y) + \nabla_{y^{h'}} \cdot J_{y^{h'}}^{h,h'}(x,y) = 0 \quad (14)$$

where

$$J_{x^h}^{h,h'}(x,y) = \frac{1}{\gamma^h(x)} \left[\frac{\bar{f}^{h,h'}(x,y)}{M^h} - \varepsilon^h \nabla_x \right] c^{h,h'}(x,y),$$

$\bar{f}^{h,h'}(x,y)$ is the average force on an ion of species h located at x , given an ion of species h' located at y , and $J_{y^{h'}}^{h,h'}$ is given by a similar expression.

For the case of pair-wise additive forces, this force can be simplified to

$$\bar{f}^{h,h'}(x,y) = f_{ed}^h(x) + f^{h,h'}(x,y) + \bar{f}_{SR}^{h,h'}(x,y) - e z^h \nabla_z \bar{\phi}^{h,h'}(z|x,y) \Big|_{z=x} \quad (15)$$

where $\bar{f}_{SR}^{h,h'}$ and $\bar{\phi}^{h,h'}$ are the higher order analogues of (9) and (10) which depend on the higher order conditional concentrations $c^{h''|h,h'}$. Thus, the determination of the forces $\bar{f}^{h,h'}(x,y)$ requires the determination of the triplet densities $c^{h,h',h''}(x,y,z)$.

Similarly, it is possible to write an equation for the triplet density, whose average forces depend on yet higher conditional densities. Thus, we obtain an *infinite* hierarchy of conditional Poisson and Nernst-Planck type equations, all defined in finite domains. The resulting equations are very similar to those used in the study of macroscopic bulk dynamical properties of electrolytes [6], where the time dependence of similar equations is considered in infinite domains. In these studies, closure relations between the triplet and pair densities, similar to those of equilibrium statistical mechanics, are employed in order to compute the average forces [9].

In our case, however, since we are concerned with a *finite* system in non-equilibrium, a closure relation between the triplet and the pair densities is not enough to close the system. Specifically, the Smoluchowski type equation (14) is defined in the finite domain $(\mathbf{x}, \mathbf{y}) \in \Omega \times \Omega$. Therefore, to uniquely determine its solution, boundary conditions have to be prescribed on the domain boundaries, e.g. for $(\mathbf{x}, \mathbf{y}) \in \partial\Omega \times \Omega$ and $(\mathbf{x}, \mathbf{y}) \in \Omega \times \partial\Omega$. Only after these boundary conditions are specified, the pair concentration $c^{h,h'}(\mathbf{x}, \mathbf{y})$ is completely determined, provided the forces $\bar{f}^{h,h'}(\mathbf{x}, \mathbf{y})$ are known. As in the case of the single ion densities, the boundary conditions for the pair densities should also be determined by the action of the feedback mechanism. For the single ion densities, the assumption that the feedback mechanism keeps an average fixed concentration on the domain boundaries leads to the natural concentration boundary conditions (13). The derivation of boundary conditions for the pair concentrations, as well as for higher order densities, requires a more detailed description of the feedback mechanism [10].

3.3 The PNP System Revisited

The simplest possible closure is $c^{h|h}(y|x) = c^{h'}(y)$. This approximation, that assumes independence of ions and thus neglects ion-ion finite size effects, recovers the (unconditional) PNP system used so far, but with an additional force term, f_{ed} , the dielectric self force on a single ion near dielectric interfaces. This term represents the forces on a single ion by surface charges induced by the ion itself at dielectric interfaces [8], [5].

Thus, the standard PNP system, which neglects both the discreteness of charge and the finite size of ions, is not valid neither near dielectric interfaces nor in confined regions [5], a property that recently has also been observed in simulations [11].

4 DISCUSSION

The main result of this paper is a coupled system of Poisson and Nernst-Planck type equations, containing conditional and unconditional charge densities and potentials. The main difference from the PNP system

is the inclusion of molecular details, such as finite size effects and the dielectric force on a discrete ion.

While traditional molecular models consider equilibrium systems based on the partition function and thus contain no dynamics, our underlying molecular model is based on particle *trajectories*, and can thus describe non-equilibrium systems governed by diffusion. Indeed, when equilibrium (no-flux) boundary conditions are imposed on the C-PNP system, the BBGKY hierarchy of equilibrium statistical mechanics is recovered. Thus, the C-PNP system is a non-equilibrium generalization of this hierarchy and its conditional densities are the non-equilibrium analogues of the well studied pair correlation functions of equilibrium statistical mechanics. In contrast to standard PNP, the C-PNP system includes the finite size of ions, which are known from equilibrium theories to cause first order effects on bulk properties of electrolytes [6]. We note that the importance of excluded volume effects has been recently observed in the context of ion channels, where models including the finite size of ions are able to predict measured selectivity of L-type calcium channels [12].

Finally, we note that our work can also serve as a part of a multi-scale analysis, in which the local diffusion coefficients and pair correlation functions of our effective equations are the output of more detailed molecular dynamics simulations.

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