

Ions in Solutions and Protein Channels

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Abstract

Flow of charge within an ion channel is considered. Continuum models which describe the distribution of mobile ionic charge are presented with dimensional analysis used to derive simplified solutions. The question of accounting for the transition from regions where continuum models are adequate to regions where individual molecules must be considered is also discussed.

1 Introduction to basics of ion channels

The study group considered the problem of determining mathematical models that describe how ions are transported through a relatively narrow channel. The main focus of the work was on calcium channels and their particular behaviour.

1.1 Outline of report structure and approach

The report starts by considering the “classical” view of the flow of ions in an electrolyte solution and its application to flow in a channel. The approach is to take a continuum view of the problem with spatially varying average ion concentrations and electric fields. The basis was therefore the system of equations typically referred to as the Poisson-Nernst-Planck (PNP) equations. The study group work concentrated on finding approximate solutions to these equations relevant to a channel using nondimensional arguments and asymptotic procedures. One of the most important aspects is to understand how the presence of a very few fixed charges held within the protein at the narrowest part of the channel can cause the observed gating phenomena.

The second part of the report considers the behaviour of the electrolyte very close to the narrowest part of the channel. The lengthscales here are so small that a continuum approach is of questionable validity. The study group looked at various problems to study the individual ions accounting not only for the electric field and the random variations due to temperature, which are included in an average manner in the PNP model, but also the Lennard-Jones forces that ensure that the finite size of the ions is accounted for. The channel typically contains only two ions at any time and theoretical methods for studying these are developed and questions raised as to how these might be smoothly matched into regions where PNP is valid.

2 Analysis of PNP approximation to current flow

The PNP model of an electrolyte typically applies to relatively slow movement so that magnetic fields are unimportant and hence the electric field is governed by the Poisson equation

$$\nabla \cdot (\epsilon \nabla \phi) = q A_v (n - p) \quad (2.1)$$

where the unknowns are the electric potential ϕ , the concentration of positively charged ions p and the concentration of negatively charged ions n (for the purposes of this report we assume that all the ions have unit valency). The parameters are q , the charge on an electron, and A_v , the Avogadro number. Finally the permeability of the electrolyte ϵ is known to be a strong function of the electrolyte concentration.

The motion of the ions within the electrolyte is controlled by the electric field experienced by the ion and by diffusion due to random thermal variations. Equations for the flux of negative ions n and positive ions p are respectively

$$J_n = -D_n \left(\nabla n - \frac{q}{kT} n \nabla \phi \right) \quad (2.2)$$

and

$$J_p = -D_p \left(\nabla p + \frac{q}{kT} p \nabla \phi \right) \quad (2.3)$$

where D_n and D_p are the diffusion coefficients of the respective ions, k is the Boltzmann constant and T is the temperature (measured in K). Note that $k = Rq/F$ where R is the universal gas constant and F is Faraday's constant. Equations (2.1)-(2.3) are closed by requiring conservation of both negative and positive ions

$$n_t + \nabla \cdot J_n = 0 \quad (2.4)$$

$$p_t + \nabla \cdot J_p = 0. \quad (2.5)$$

3 Nondimensionalisation

The system of equations above can be nondimensionalised in a number of ways. There have been a number of approaches use in the semiconductor device literature and some of the asymptotic analysis presented in these may be very suitable for use in analysing behaviour in a channel. Examples from semiconductor theory can be seen in Please [1], Ward [2-3] and Markowich, Ringhofer and Schmeiser [5-14]. Note that, unlike in most semiconductor devices, within the channel there is not much fixed charge and the externally applied voltage is typically very close in size to the thermal voltage kT/q , hence the approach of Schmeiser and others [12-14] may be more appropriate than many others who consider large applied voltages and large dopant densities.

Typical boundary conditions on the sixth order problem (2.1)-(2.5) consist of data on ϕ , n and p in the far field while on confining surfaces there will be conditions on $J_n \cdot \mathbf{N}$, $J_p \cdot \mathbf{N}$ and $\partial\phi/\partial N$ (where \mathbf{N} is a unit normal to the surface). Ion fluxes may thus be thought

to arise as a consequence of differences in ion concentrations and in potential across the domain and we scale J_n and J_p accordingly. In addition we know that, throughout most of the domain, approximate charge neutrality $p \simeq n$ holds which suggests that n and p should be scaled with the same constant Π . The crucial assumption we make in this non-dimensionalisation is that ϕ scales like kT/q (the thermal voltage). If changes in ϕ are less than kT/q diffusion is dominant, and a rather dull problem results while if the changes in ϕ are much greater than kT/q then advection is dominant. The scaling we have chosen for ϕ thus corresponds to a limit in which both advection and diffusion are in balance; it also turns out to be a sensible choice given the typical sizes of the externally applied voltage across cell membranes.

The nondimensionalisation proceeds as follows:

$$\begin{aligned} x &= L\bar{x}, & t &= \frac{L^2}{D_n}\bar{t}, & \phi &= \frac{kT}{q}\bar{\phi}, & J_n &= \frac{D_n\Pi}{L}\bar{J}_n, \\ J_p &= \frac{D_n\Pi}{L}\bar{J}_p, & n &= \Pi\bar{n}, & p &= \Pi\bar{p}, & \varepsilon &= \varepsilon_w\bar{\varepsilon}. \end{aligned}$$

where L is the macroscopic lengthscale of interest and ε_w is the typical electrical permeability. Substituting into (2.1)-(2.5), and forgetting the overbar notation for the remainder of this section to simplify typesetting, we get

$$\nabla \cdot (\varepsilon \nabla \phi) = \Gamma(n - p) \tag{3.1}$$

$$J_n = -(\nabla n - n \nabla \phi) \tag{3.2}$$

$$J_p = -\nu(\nabla p + p \nabla \phi) \tag{3.3}$$

$$n_t + \nabla \cdot J_n = 0 \tag{3.4}$$

$$p_t + \nabla \cdot J_p = 0. \tag{3.5}$$

Here there are two parameters

$$\Gamma = \frac{q^2 A_v \Pi L^2}{\varepsilon_w k T} \quad \text{and} \quad \nu = \frac{D_p}{D_n}. \tag{3.6}$$

We can then consider the size of these parameters using the data for a typical ion channel given in 1. Here Γ represents the square of the ratio of the size, L of the channel and the intrinsic Debye length of the electrolyte. In fact the Debye length is typically a nanometer. Thus if we nondimensionalise with the typical radius of the neck of the channel ($L = O(10^{-9})\text{m}$) $\Gamma = O(1)$ whereas if we nondimensionalise with its depth ($L = O(10^{-7})\text{m}$) $\Gamma \gg 1$. Typically ν (the ratio of the diffusivities) has a value near 1.

Parameter	Size	Units
j	$10^2 - 10^3$	$\text{mol m}^{-2}\text{s}^{-1}$
D_n	10^{-10}	m^2s^{-1}
D_p	10^{-10}	m^2s^{-1}
q	1.6×10^{-19}	Amp s
k	1.38×10^{-23}	J K ⁻¹
T	300	K
A_v	6.2×10^{26}	mol^{-1}
Π	10^2	mol m^{-3}
L	$10^{-9} - 10^{-7}$	m
ε_0	8.85×10^{-12}	Amp s V ⁻¹ m ⁻¹
ε_w	7.08×10^{-10}	Amp s V ⁻¹ m ⁻¹
T	300	K

Table 1: Data for a typical electrolyte and a channel

3.1 Remark on boundary conditions

A rough sketch of the region to be considered in is given in figure 1. Here there is a protein sitting in a lipid layer with electrolyte around about. The region of greatest interest here is the relatively conical region forming the ion channel within the protein and also the neck of the protein where the fixed charges sit.

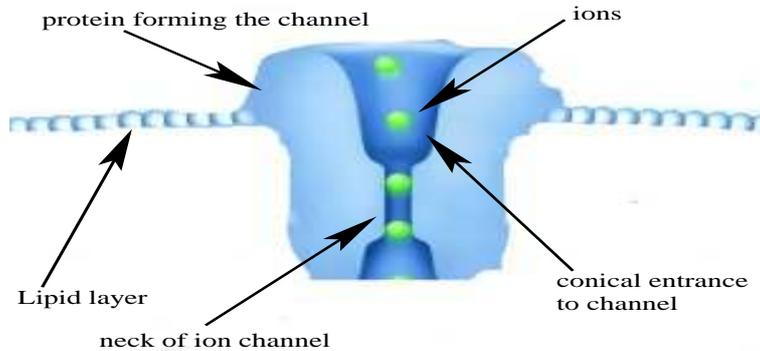


Figure 1: A rough sketch of a protein forming an ion channel (adapted from campus.lakeforest.edu/~light/teaching.html)

The dielectric constant of water is roughly $80\varepsilon_0$. This is extremely large in comparison to most other materials and in particular to that of the protein. At the interface between the protein and the electrolyte (mainly water) the following jump conditions hold for the

electric field, $\mathbf{E} = -\nabla\phi$:

$$[\varepsilon\mathbf{E} \cdot \mathbf{N}] = 0, \quad [\mathbf{E} \times \mathbf{N}] = \mathbf{0}.$$

where, as before, \mathbf{N} is the outward normal to the electrolyte. Given the disparity in the sizes of ε in the two materials, and assuming there is no large field within the protein, we can impose the asymptotic boundary condition

$$\mathbf{E} \cdot \mathbf{N}|_{\partial\Omega} = 0 \Rightarrow \left. \frac{\partial\phi}{\partial N} \right|_{\partial\Omega} = 0.$$

at the edge of the electrolyte. The other boundary conditions required at the edge of the electrolyte are zero flux conditions on n and p

$$\left. \frac{\partial n}{\partial N} - n \frac{\partial\phi}{\partial N} \right|_{\partial\Omega} = 0, \quad \left. \frac{\partial p}{\partial N} + p \frac{\partial\phi}{\partial N} \right|_{\partial\Omega} = 0$$

Putting all these conditions together we have

$$\left. \frac{\partial\phi}{\partial N} \right|_{\partial\Omega} = 0, \quad \left. \frac{\partial n}{\partial N} \right|_{\partial\Omega} = 0, \quad \left. \frac{\partial p}{\partial N} \right|_{\partial\Omega} = 0. \quad (3.7)$$

3.2 Equilibrium solution

One of the simplest situations to consider for an electrolyte is equilibrium. In such a case there is no flow of the charges ($J_n \equiv J_p \equiv 0$). Such a case would occur if the channel were blocked so that no ions could flow through. The problem considered in the meeting was where the upper part of the channel was a cone with the blocked channel at a distance $r = \delta$ from the apex. It was assumed that the ions went to a concentration $n = p = 1$ as $r \rightarrow \infty$. In addition it was assumed that the simplified boundary conditions (3.7) hold. In this case we find first that

$$n = \exp(\phi) \quad p = \exp(-\phi) \quad (3.8)$$

so that the ions have a Boltzmann distribution in energy. Assuming that the permeability is constant the electric field is then governed by

$$\nabla^2\phi = 2\Gamma \sinh \phi \quad (3.9)$$

with the boundary condition $\phi \rightarrow 0$ as $r \rightarrow \infty$. Finally we need to consider what the few charges in the protein at the blocked channel can do. To represent these charges we impose

$$\left. \frac{\partial\phi}{\partial r} \right|_{r=\delta} = \frac{-\alpha}{r^2} \quad \text{on } r = \delta \quad (3.10)$$

where α indicates the number of charges.

This problem can be studied in various asymptotic limits. One case considered was when $\delta \rightarrow 0$ with other parameters taken to be $\mathcal{O}(1)$. In this case there are three separate regions of the problem namely the outer region where $n \approx p$ and ϕ is exponentially small an intermediate region where the lengthscale is determined by the size of the neck region $r = \mathcal{O}(\delta)$, and finally a very narrow layer adjacent to the neck of the channel where $r = \delta + \mathcal{O}(1/\ln(1/\delta))$.

Hence the behaviour can be found to be almost entirely concentrated in a very narrow layer adjacent to the start of the neck. In practice the narrow layer is smaller than either the minimum channel diameter or the size of an individual diameter. Hence this general behaviour indicated that, at least in equilibrium, the electrolyte is almost entirely “charge neutral” (with $n = p$) and there may only be a few ions needed to shield the effect of the fixed charges.

3.2.1 Neutral region solution

Motivated in part by the previous observation concerning the equilibrium case and also by the small Debye length, analysis was done of the behaviour of the solutions to the problem where there is charge neutrality ($n = p$). This is an excellent model of the behaviour a reasonable distance from the narrowest part of the channel and is sometime referred to as describing the “access resistance” to the channel. To generate analytical formulae we shall assume that the solution is in steady state.

We assume that the length scale of interest is sufficiently large that the Poisson equation for the electric field (3.1) reduces to

$$n = p . \tag{3.11}$$

This is expected to be true for lengthscales larger than the radius of the neck region. The equations for the movement of the charges and the conservation of ions (3.2) and (3.3), in equilibrium, dictate that

$$0 = \nabla^2 n - \nabla \cdot (n \nabla \phi) \tag{3.12}$$

$$0 = \nabla^2 p + \nabla \cdot (p \nabla \phi) . \tag{3.13}$$

By adding and using $n = p$ it follows that n satisfies the Laplace equation

$$\nabla^2 n = 0 \tag{3.14}$$

and, once n is known, then ϕ satisfies the linear equation

$$\nabla \cdot (n \nabla \phi) = 0 . \tag{3.15}$$

Now consider a region of electrolyte bounded by a protein with the property that its dielectric constant is much less than that of the electrolyte. In light of the discussion in §3.1 we impose the simplified boundary conditions (3.7) on n and ϕ . In particular we find that we can take

$$\phi = A + B \ln n \tag{3.16}$$

where A and B are constants, since this satisfies (3.15), given (3.14), and ensures that when the normal gradient of n is zero we will also find the normal gradient of ϕ will be zero. This special solution can also be written in the form

$$n = \gamma \exp(\beta\phi) \quad (3.17)$$

with γ and β constants, showing that n (and hence p) are Boltzmann distributions in this case but that the steepness of the distribution has been changed from its equilibrium state.

An example: ion flux through an uncharged ion channel

Here we consider an infinite ion channel defined by a protein surface given by a hyperboloid. We assume that there are no fixed charges in the neck and use the model above to calculate the flux of ions through the neck as a function of the potential drop across the membrane and the concentrations of ions either side of the membrane. Consider an infinite impermeable boundary (the protein) to the domain lying inside the hyperboloid

$$\frac{r^2}{a^2 \cos^2 \Theta} - \frac{z^2}{a^2 \sin^2 \Theta} = 1,$$

(the ion channel). Here r and z are cylindrical polar coordinates and a and Θ parametrise the hyperboloid. The surface $z = 0$ $r < a$ corresponds to the neck of the channel and there are regions $z > 0$ and $z < 0$ corresponding to the entrances to the channel on either side. Note that a hyperboloid gives a reasonable approximation to the conical shape of the protein associated with an ion channel.

We introduce oblate spheroidal coordinates (ξ, η) such that

$$r = a \cosh \xi \cos \eta \quad z = a \sinh \xi \sin \eta.$$

Lines of constant ξ are thus given by the oblate spheroids

$$\frac{r^2}{\cosh^2 \xi} + \frac{z^2}{\sinh^2 \xi} = a^2$$

while those of constant η are given by the hyperboloids

$$\frac{r^2}{\cos^2 \eta} - \frac{z^2}{\sin^2 \eta} = a^2.$$

The upper half of the domain thus lies in $\pi/2 > \eta > \Theta$, $\xi > 0$. In these coordinates we thus have

$$\nabla^2 n = \frac{1}{a^2(\sinh^2 \xi + \sin^2 \eta) \cosh \xi} \frac{\partial}{\partial \xi} \left(\cosh \xi \frac{\partial n}{\partial \xi} \right) + \frac{1}{a^2(\sinh^2 \xi + \sin^2 \eta) \cos \eta} \frac{\partial}{\partial \eta} \left(\cos \eta \frac{\partial n}{\partial \eta} \right).$$

while the boundary condition $\partial n / \partial N = 0$ on $\eta = \Theta$ translates to

$$\left. \frac{\partial n}{\partial \eta} \right|_{\eta=\Theta} = 0.$$

It thus seems obvious to look for a solution to $\nabla^2 n = 0$ with these boundary conditions of the form $n = n(\xi)$ and indeed we find one of the form

$$n = \frac{n_+ - n_-}{2} \left(\frac{4}{\pi} \arctan(e^\xi) - 1 \right) + \frac{n_+ + n_-}{2}, \quad (3.18)$$

Here the constants in the solution have been chosen so that $n \rightarrow n_+$ as $\xi \rightarrow +\infty$ and $n \rightarrow n_-$ as $\xi \rightarrow -\infty$. Following (3.16) we write

$$\phi = A + B \ln n \quad (3.19)$$

and applying the boundary conditions $\phi \rightarrow \phi_+$ as $\xi \rightarrow +\infty$ and $\phi \rightarrow \phi_-$ as $\xi \rightarrow -\infty$ gives

$$\phi = \frac{(\phi_+ - \phi_-) \ln n + (\phi_- \ln n_+ - \phi_+ \ln n_-)}{\ln n_+ - \ln n_-} \quad (3.20)$$

In the special case $n^+ = n^-$ we find that n is constant across the channel. The equation for ϕ is $\nabla^2 \phi = 0$ and the solution for ϕ is thus given by (3.18) with n replaced everywhere by ϕ .

The flux of negative n ions through the funnel (created by the hyperboloid) can be evaluated by considering the flux through the surface $\xi = 0$.

$$J_n = -(\nabla n - n \nabla \phi) = (B - 1) \nabla n = \frac{(B - 1)}{a(\sin^2 \eta + \sinh^2 \xi)^{1/2}} \frac{\partial n}{\partial \xi} \mathbf{e}_\xi,$$

where B is defined by the relations (3.19) and (3.20). Notice also that $J_p = -\nu(B + 1)\nabla n$. Thus

$$J_n = \left(\frac{\phi_+ - \phi_-}{\ln n_+ - \ln n_-} - 1 \right) \nabla n \quad (3.21)$$

$$= \left(\frac{\phi_+ - \phi_-}{\ln n_+ - \ln n_-} - 1 \right) \left(\frac{2(n_+ - n_-)}{\pi a(\sin^2 \eta + \sinh^2 \xi)^{1/2}} \right) \frac{e^\xi}{1 + e^{2\xi}} \mathbf{e}_\xi. \quad (3.22)$$

It follows that the total flux F_n of negative ions up through the surface $\xi = 0$ (*i.e.* $z = 0$) is

$$F_n = - \int_{\eta=\pi/2}^{\Theta} (J_n|_{\xi=0} \cdot \mathbf{e}_z) 2\pi a^2 \cos \eta \sin \eta \, d\eta \quad (3.23)$$

$$F_n = 2a \int_{\Theta}^{\pi/2} \left(\frac{\phi_+ - \phi_-}{\ln n_+ - \ln n_-} - 1 \right) (n_+ - n_-) \cos(\eta) \, d\eta \quad (3.24)$$

$$F_n = 2a \left(\frac{\phi_+ - \phi_-}{\ln n_+ - \ln n_-} - 1 \right) (n_+ - n_-) (1 - \sin \Theta), \quad (3.25)$$

while that of positive ions is

$$F_p = -2a\nu \left(\frac{\phi_+ - \phi_-}{\ln n_+ - \ln n_-} + 1 \right) (n_+ - n_-) (1 - \sin \Theta). \quad (3.26)$$

Discussion.

- Note first that the charge neutrality assumption breaks down only if $\nabla^2\phi$ becomes very large at some point (see equation (3.1)). Looking at the result for ϕ (3.20) this will occur only if

$$\nabla^2(\ln n) = -\frac{|\nabla n|^2}{n^2} = -\frac{1}{n^2} \frac{1}{a^2(\sin^2 \eta + \sinh^2 \xi)} \frac{(n^+ - n^-)^2}{\pi^2 \cosh^2 \xi}$$

becomes large. Thus there is no need to introduce a Debye (boundary) layer unless the angle of the hyperboloid is $\Theta = 0$ (corresponding to a membrane with a hole in it).

- The fluxes of negative and positive ions through the channel are given by the formulae (3.25) and (3.26) respectively. Without loss of generality we can assume that $n^+ > n^-$. It follows that

$$\begin{aligned} F_n < 0 \quad F_p > 0 & \quad \text{for} \quad \phi_+ - \phi_- < -\ln(n_+/n_-), \\ F_n < 0 \quad F_p < 0 & \quad \text{for} \quad \ln(n_+/n_-) > \phi_+ - \phi_- > -\ln(n_+/n_-), \\ F_n > 0 \quad F_p < 0 & \quad \text{for} \quad \phi_+ - \phi_- > \ln(n_+/n_-), \end{aligned}$$

Thus even in an uncharged ion channel the cell is able to control, to some extent, which ions flow in which direction by altering the potential difference across the channel. In particular it is able to arrange the flow of ions so that (i) $F_p = 0$ and $F_n < 0$ and (ii) $F_p < 0$ and $F_n = 0$. However, it cannot cause a flow in which one species of ion flows against the gradient in concentration without giving a flux of the other ion species in the same direction as this gradient.

- It may be mathematically interesting to see if it is possible to extend this solution method to consider time variations in special cases such as $\nu = 1$. This might be done by taking the coefficients A and B in (3.19) to be time-dependent with $A = A(t)$ and $B = B(t)$.

3.3 Slowly varying channels

To gain some insight into the gating behaviour of the channel an idealised problem was considered in which it was assumed that the PNP theory was applicable everywhere including in the channel. The charges in the channel were taken to be represented by some distribution of fixed charges within the channel in a manner similar to that used for dopant in semiconductor modelling. It was assumed that the entire channel could be taken to be “slowly varying” where the slope of the channel remained small and the problem could easily be characterised by a cross-sectional area $A(z)$ where z is the distance through the channel. We are interested in the behaviour of the problem close to the fixed charges and so we take a length scale similar to the intrinsic Debye length and hence here $\Gamma = 1$. In addition because the region is long and thin the current will be constant and hence the current densities are, as yet unknown, constants f_n and f_p .

The problem to be solved consists of the area averaged equations

$$\frac{1}{A(z)} (A(z)\phi_z)_z = (n - p) + C(z) \quad (3.27)$$

$$f_n/A(z) = -(n_z - n\phi_z) \quad (3.28)$$

$$f_p/A(z) = -\nu(p_z + p\phi_z) \quad (3.29)$$

with conditions that:

$$\text{as } z \rightarrow -\infty : n \rightarrow 1, p \rightarrow 1, \phi \rightarrow 0$$

$$\text{as } z \rightarrow \infty : n \rightarrow n_1, p \rightarrow p_1, \phi \rightarrow \Phi.$$

The problem is either stated by giving the currents f_p and f_n with n_1 and p_1 to be found, or by specifying the far-field concentrations n_1 and p_1 and finding the currents.

To represent the charges in the channel the function $C(z)$ was taken to be zero everywhere except in a small region where it was constant.

This problem was solved by numerical procedures involving shooting and graphs of the solution for the case where $A(z) = 1 + z^2$, $\nu = 1$, $\Phi = -1$, $f_n = 0.1$ and $f_p = 0.5$ for two different cases of the fixed charge, $C(x)$. The solutions are given graphically in figure 2

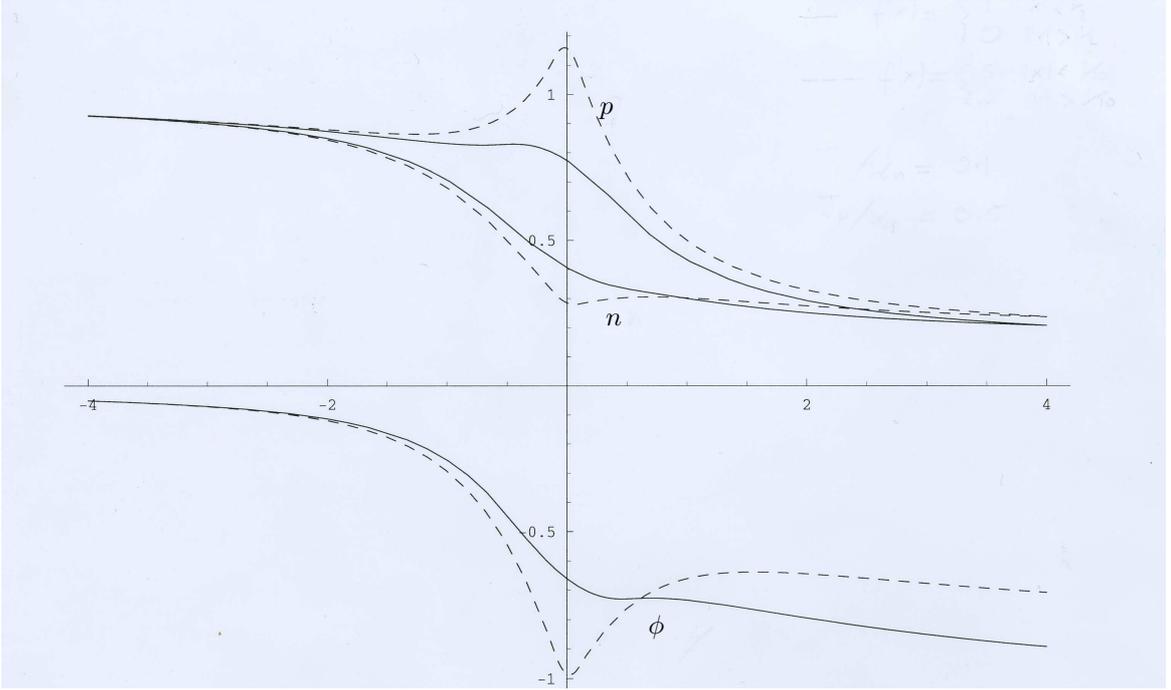


Figure 2: Electric potential, ϕ and ion concentrations, n and p , for an area averaged PNP model of the channel. Solid lines are when $C(z) = 1$ for $|z| \leq 0.5$ Dotted lines are when $C(z) = 5$ for $|z| \leq 0.1$

4 Model of movement in the channel

4.1 Governing equations

Models that account for the motion of individual molecules start with a Langevin equations for each of the molecules. This equations describes the balance of forces on the molecule. For statistical mechanics problems, the forces balance with the molecule acceleration but for ions there is a very large drag force on the particles and an “overdamped” version of the equation is used with acceleration neglected (note this reduced version of the equations is also used in most modelling of financial products). Considering a system of N molecules, for each molecule we write

$$\gamma \dot{\mathbf{x}}_i = \mathbf{F}_i + \sqrt{2kT\gamma} \dot{\mathbf{w}}_i \quad (4.1)$$

where γ is the damping coefficient, \mathbf{x}_i are the position of the i 'th molecule, \mathbf{F}_i is the force acting on the molecule and $\dot{\mathbf{w}}_i$ is the random thermal agitation, usually taken to be white noise. A common notation is to refer to the deterministic part of the equation as determining the velocity so that

$$\gamma \mathbf{v}_i = \mathbf{F}_i \quad (4.2)$$

There are of course a number of different types of molecules in the electrolyte but we only consider the ions. We presume that there are two forces on these, one due to the local electric field and the other due to local interaction with neighbours taken to be the Lennard-Jones force which will ensure the finite size of the ions is represented. Hence the force can be written as

$$\mathbf{F}_i = -z_i \nabla \phi + \sum_{i \neq j} L(|\mathbf{x}_i - \mathbf{x}_j|) \quad (4.3)$$

where z_i is the valency of the molecules and the second function is the interaction term, which depends on the position of all the other molecules in the system. Typically the Lennard-Jones force is considered to take the form

$$L(x) = D \left(\frac{\sigma^6}{x^{12}} - \frac{1}{x^6} \right) \quad (4.4)$$

where σ is a constant length for each molecule. To this equation we must add the Poisson equation that will determine the electric field. There are of course issues relating to how to properly account for the observed variation of the permeability with ion concentration but here we simply assume this can be taken to be locally constant. The equation is therefore

$$\nabla \cdot (\epsilon \nabla \phi) = - \sum_i z_i \delta(\mathbf{x} - \mathbf{x}_i) - \sum_k z_k \delta(\mathbf{x} - \mathbf{X}_k) \quad (4.5)$$

where \mathbf{X}_k are the positions of the fixed charges in the protein.

Rather than simulate the motion of every particle, a common way to study the motion of the particles is to consider the probability distribution of the position of the particles. Introducing the notation

$$f(\mathbf{x}_1, \mathbf{x}_1, \dots, \mathbf{x}_N, t) \quad (4.6)$$

as the probability distribution at time t of the first particle being at position \mathbf{x}_1 the second particle being at position \mathbf{x}_2 and so on, the probability distribution satisfies the Fokker-Planck equation

$$\frac{\partial f}{\partial t} + \nabla_{\mathbf{x}_i} \cdot (\mathbf{v}_i f) = \delta \nabla_{\mathbf{x}_i}^2 f. \quad (4.7)$$

This represents the behaviour of the system with the advection term due to the deterministic velocities \mathbf{v}_i and the Laplacian operator arising from the white noise. Note that in this equation the ‘‘spatial derivatives’’ are with respect to all the variables representing the position of the particles and therefore, if there are N particles, there are N spatial variables to consider.

If we consider (4.1) with (4.3) then we can identify velocities due to the electric field term, due to the Lennard-Jones term and due to the noise. For the velocity due to the electric field we note that the solution to the equation (4.5) can be written in the form

$$\epsilon \nabla \phi(\mathbf{x}_i) = - \sum_{j \neq i} z_j \nabla G(\mathbf{x}_i - \mathbf{x}_j) - \sum_k z_k \nabla G(\mathbf{x}_k - \mathbf{X}_i) \quad (4.8)$$

where G is the Green’s function for the Laplacian. From this we find that the velocity due to the electric field is therefore

$$\dot{\mathbf{x}}_i = \frac{z_i}{\gamma \epsilon} \left(\sum_{j \neq i} z_j \nabla G(\mathbf{x}_i - \mathbf{x}_j) + \sum_k z_k \nabla G(\mathbf{x}_k - \mathbf{X}_i) \right) \quad (4.9)$$

Unfortunately the Lennard-Jones force does not satisfy a simple linear field equation and it is not therefore possible to write the resulting force in any simple manner.

Solving the Fokker-Planck equations for any adequate number of particles is a substantial task due to the dimensionality of the problem. Hence a further simplification is made by looking at the marginal distribution functions for the particles. From here on we consider only positively charged ions and we ignore the Lennard-Jones forces. The extension to positive and negative ions is straight forward. We define the first marginal distribution function $f_1(\mathbf{x}_1, t)$ to be the probability of finding molecule 1 at position \mathbf{x}_1

$$f_1(\mathbf{x}_1, t) = \frac{1}{Q^{N-1}} \iiint f(\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N, t) d\mathbf{x}_2 \dots d\mathbf{x}_N \quad (4.10)$$

where Q is the volume of the domain. By integrating the Fokker-Planck equation we find that f_1 satisfies the equation

$$\frac{\partial f_1}{\partial t} + \nabla_{\mathbf{x}_1} \cdot \mathbf{B} = \delta \nabla_{\mathbf{x}_1}^2 f_1 \quad (4.11)$$

which is an equation in just the \mathbf{x}_1 space dimension and time. However the function \mathbf{B} is given by

$$\mathbf{B} = \frac{1}{\gamma \epsilon Q^{N-1}} \iiint \sum_{j \neq 1} \nabla G(\mathbf{x}_1 - \mathbf{x}_j) f(\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N, t) d\mathbf{x}_2 \dots d\mathbf{x}_N \quad (4.12)$$

which can be written in the form

$$= \frac{N-1}{\gamma\epsilon Q} \int \nabla G(\mathbf{x}_1 - \mathbf{x}_2) f_2(\mathbf{x}_1, \mathbf{x}_2, t) d\mathbf{x}_2 \quad (4.13)$$

by introducing the “two-particle distribution function”

$$f_2(\mathbf{x}_1, \mathbf{x}_2, t) = \frac{1}{Q^{N-2}} \iiint f(\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N, t) d\mathbf{x}_3 \dots d\mathbf{x}_N \quad (4.14)$$

This gives the probability of particle 1 being at position \mathbf{x}_1 and particle 2 being at \mathbf{x}_2 . An equation can then be developed for f_2 from the Fokker-Planck equation but this solution then depends on f_3 , the three-particle distribution. This dependency of one average on a higher-order correlation is the classical “closure problem” inherent in such averaging procedures. A common method of closing the problem is to assume that at some point the probabilities are independent. For example it might be reasonable to assume that particles act independently and hence

$$f_2(\mathbf{x}_1, \mathbf{x}_2, t) = f_1(\mathbf{x}_1, t) f_1(\mathbf{x}_2, t) \quad (4.15)$$

In this case it is then possible to determine \mathbf{B} in the form

$$\mathbf{B} = \frac{N-1}{\gamma\epsilon Q} \int \nabla G(\mathbf{x}_1 - \mathbf{x}_2) f_1(\mathbf{x}_1) f_1(\mathbf{x}_2, t) d\mathbf{x}_2 \quad (4.16)$$

which can be readily integrated to give

$$\mathbf{B} = \frac{N-1}{\gamma\epsilon Q} f_1(\mathbf{x}_1) \iint \nabla G(\mathbf{x}_1 - \mathbf{x}_2) f_1(\mathbf{x}_2, t) d\mathbf{x}_2 \quad (4.17)$$

Then writing $p = (N-1)f_1(x_1)/Q$, we find that

$$\frac{\partial p}{\partial t} + \nabla \cdot (\mathbf{v}p) = \delta \nabla^2 p, \quad (4.18)$$

with

$$\mathbf{v} = \frac{1}{\gamma\epsilon} \int \nabla G(\mathbf{x} - x') p(x') dx' \quad (4.19)$$

This can be written as

$$\nabla(\epsilon \nabla \phi) = -p \quad \mathbf{v} = -\nabla \phi \quad (4.20)$$

which is of course the PNP model.

4.2 Simplified situations

In the bulk of the electrolyte, away from the narrowest point, the PNP model gives a good description of the behaviour of the ion. Within the narrow part of the channel and very close to this region we need to account for individual particles. Various suggestions

were put forward as to how this could be achieved and still allow some progress toward understanding the behaviour.

One suggestion is that the narrowest part of the channel will attract a number of ions determined by the number of fixed charges while the PNP modelling indicates that except for a very narrow region near these fixed charges the electrolyte will be charge neutral. For simplicity the case of two single fixed charges in the channel and ions with a single charge each was considered. Here we anticipate that there will almost always be just two ions in the narrow part of the channel. Hence, when considering charged points \mathbf{x}_1 , \mathbf{x}_2 etc., if the points are outside the channel then we can consider the particles to be independent while when they are in the channel we must account for their interaction. Since the maximum number of particle in the channel is two we may be able to consider the two-particle interactions for these but, to solve our closure problem, we may make the assumption that the three-particle interactions can be modelled assuming the third particle is out in the PNP valid region. Hence if \mathbf{x}_1 , \mathbf{x}_2 are in the channel and \mathbf{x}_3 is outside the channel then

$$f_3(\mathbf{x}_1, \mathbf{x}_2, \mathbf{x}_3, t) = f_2(\mathbf{x}_1, \mathbf{x}_2, t)f_1(\mathbf{x}_3, t) \quad (4.21)$$

The equation for f_2 is then

$$\frac{\partial f_2}{\partial t} + \nabla_{\mathbf{x}_1} \cdot \mathbf{B}_1 + \nabla_{\mathbf{x}_2} \cdot \mathbf{B}_2 = \delta (\nabla_{\mathbf{x}_1}^2 f_2 + \nabla_{\mathbf{x}_2}^2 f_2) \quad (4.22)$$

where

$$\mathbf{B}_1 = \frac{1}{\gamma\epsilon} \nabla G(\mathbf{x}_1 - \mathbf{x}_2) + \frac{N-2}{\gamma Q} f_2(\mathbf{x}_1, \mathbf{x}_2) \iint \nabla G(\mathbf{x}_1 - \mathbf{x}_3) f_1(\mathbf{x}_3, t) d\mathbf{x}_3 \quad (4.23)$$

$$\mathbf{B}_2 = \frac{1}{\gamma\epsilon} \nabla G(\mathbf{x}_2 - \mathbf{x}_1) + \frac{N-2}{\gamma Q} f_2(\mathbf{x}_1, \mathbf{x}_2) \iint \nabla G(\mathbf{x}_2 - \mathbf{x}_3) f_1(\mathbf{x}_3, t) d\mathbf{x}_3 \quad (4.24)$$

To this it is necessary to add the Poisson equation for the electric field. This equation will have the two fixed charges and the two ions in the channel. There are some issues that arise with how to account for any third particle in this model and also what boundary conditions should be imposed (they should represent matching into the PNP region but this may require including in the model an ion of opposite charge in order to allow the solution to match into a charge neutral region). Notice also that in practice the model must account for the Lennard-Jones forces that are local and cannot be accounted for in the manner given above although the restriction of just two particles to the region of interest is anticipated to account for this. Such a model may allow us to calculate the expected flux of ions through the narrow channel by following trajectories of the ions.

5 Further Developments

The problem studied here raises a number of difficult problems. The interaction between a region where continuum models are applicable and another where the behaviour of a

few individual particles is crucial makes the matching processes very difficult. We need to identify a “simplest possible” configuration with the narrow part of the channel that may contain the crucial dynamics of such an interaction in order to gain some more insight.

There may be ways in which we can further exploit asymptotic methods perhaps using the small noise limit or the rapid change in electric permeability.

One of the most important aspects that we have tended to avoid in this report is the effect of the Lennard Jones potentials. There was considerable discussion about how these might sensibly be incorporated into the modelling and this remains an area of considerable interest.

6 Participants

The following people were involved with this problem during the study group: Nim Arinaminpathy, Chris Bell, Jon Chapman, Bob Eisenberg, Chris Farmer, Peter Howell, Marvin Jones, John King, Philip Murray, John Norbury, John Ockendon, Colin Please, Giles Richardson, Amit Singer

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